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017534-000730US
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,068	12/13/2001	Rodney A. Perkins	017534-000730US	7372

20350 7590 06/28/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

THOMPSON, KATHRYN L

ART UNIT

PAPER NUMBER

3763

DATE MAILED: 06/28/2005



Response Due 09/28/05

Please find below and/or attached an Office communication concerning this application or proceeding.

BEST AVAILABLE COPY



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

NOTICE UNDER 37 CFR 1.251 - Pending Application

☒ The file of the above-identified application cannot be located after a reasonable search. Therefore, the Office is initiating the reconstruction of the file of the above-identified application pursuant to the provisions of 37 CFR 1.251.

Applicant is given a period of **THREE (3) MONTHS** from the mailing date of this notice within which to provide a copy of applicant's record (if any) of all of the correspondence between the Office and applicant for the above-identified application (except for U.S. patent documents), a list of such correspondence, and a statement that the copy is a complete and accurate copy of applicant's record of all of the correspondence between the Office and the applicant for the above-identified application (except for U.S. patent documents), and whether applicant is aware of any correspondence between the Office and applicant for the above-identified application that is not among applicant's records.

☐ The following paper(s) pertaining to the above-identified application cannot be located after a reasonable search:

Therefore, the Office is initiating the reconstruction of such paper(s) pursuant to the provisions of 37 CFR 1.251.

Applicant is given a period of **THREE (3) MONTHS** from the mailing date of this notice within which to provide a copy of the paper(s) listed above and a statement that the copy of such paper(s) is a complete and accurate copy of applicant's record of such paper(s).

Alternatively, applicant may reply to this notice by producing applicant's record (if any) of all of the correspondence between the Office and the applicant for the above-identified application for the Office to copy (except for U.S. patent documents), and provide a statement that the papers produced by applicant are applicant's complete record of all of the correspondence between the Office and the applicant for the above-identified application (except for U.S. patent documents), whether applicant is aware of any correspondence between the Office and the applicant for the above-identified application that is not among applicant's records. Such records must be brought to the Customer Service Center in the Office of Initial Patent Examination (Crystal Plaza 2, 2011 South Clark Place, Arlington, VA 22202).

If applicant does not possess any record of the correspondence between the Office and the applicant for the above-identified application (or any copy of the paper(s) listed above), applicant must reply to this notice by providing a statement that applicant does not possess any record of the correspondence between the Office and the applicant for the above-identified application.

Failure to reply to this notice in a timely manner will result in abandonment of the above-identified application. The three-month period for reply to this notice may be extended (up to a maximum of six months) under the provisions of 37 CFR 1.136(a). However, failure to reply within this three-month period will result in a reduction of any patent term adjustment. See 37 CFR 1.704(b).

☒ A printout from PALM of the contents of the file of the above-identified application is included with this notice.

Direct the reply to this notice to:

Mail Stop RECONSTRUCTION
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Direct questions concerning this notice to:

C. Melvin Brown
571-272-4333

Carolyn Brown
Supervisory Legal Instrument Examiner
Group 3700

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PTO-2053-B (Rev. 10/03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

Att: Carolyn Brown TC 3700
RND 8611

In re Application of: _____

Application No.: _____

Filing Date: _____

Title: _____

Direct to:

Mail Stop RECONSTRUCTION
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

NOTICE UNDER 37 CFR 1.251 - Pending Application

Statement (check the appropriate box):

- ☐ The copy submitted with this reply is a complete and accurate copy of applicant's record of all of the correspondence between the Office and the applicant for the above-identified application (except for U.S. patent documents), and applicant is not aware of any correspondence between the Office and applicant for the above-identified application that is not among applicant's records.
- ☐ The copy of the paper(s) listed in the notice under 37 CFR 1.251 is/are a complete and accurate copy of applicant's record of such paper(s).
- ☐ The papers produced by applicant are applicant's complete record of all of the correspondence between the Office and the applicant for the above-identified application (except for U.S. patent documents), and applicant is not aware of any correspondence between the Office and the applicant for the above-identified application that is not among applicant's records.
- ☐ Applicant does not possess any record of the correspondence between the Office and the applicant for the above-identified application.

Date

Signature

Typed or printed name

A copy of this notice should be returned with the reply.

Burden Hour Statement: This collection of information is required by 37 CFR 1.251. The information is used by the public to reply to a request for copies of correspondence between the applicant and the USPTO in order to reconstruct an application file. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This form is estimated to take 60 minutes to complete. This time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.**

Day : Thursday
Date: 6/23/2005

PALM INTRANET

Time: 15:47:57

Content Information for 10/017068

Search Another: Application# or Patent#
PCT / / or PG PUBS #
Attorney Docket #
Bar Code #

[Appln Info](#) [Contents](#) [Petition Info](#) [Atty/Agent Info](#) [Continuity Data](#) [Foreign Data](#)

Date	Status	Code	Description
02/10/2005		LFLOST	FILE MARKED LOST
08/24/2004		WAMD	WORKFLOW INCOMING AMENDMENT IFW
02/23/2004	41	MCTNF	MAIL NON-FINAL REJECTION
02/20/2004	40	CTNF	NON-FINAL REJECTION
08/04/2003		M844	INFORMATION DISCLOSURE STATEMENT (ID
08/13/2003		FWDX	DATE FORWARDED TO EXAMINER
08/04/2003	71	A...	RESPONSE AFTER NON-FINAL ACTION
08/04/2003		XT/G	REQUEST FOR EXTENSION OF TIME - GRANTI
02/19/2003	41	MCTNF	MAIL NON-FINAL REJECTION
02/10/2003	40	CTNF	NON-FINAL REJECTION
02/06/2003		DOCK	CASE DOCKETED TO EXAMINER IN GAU
03/05/2002		M844	INFORMATION DISCLOSURE STATEMENT (ID
03/05/2002		M844	INFORMATION DISCLOSURE STATEMENT (ID
03/28/2002	30	DOCK	CASE DOCKETED TO EXAMINER IN GAU
01/03/2002	20	OIPE	APPLICATION DISPATCHED FROM OIPE
01/02/2002		COMP	APPLICATION IS NOW COMPLETE
12/31/2001		SCAN	IFW SCAN & PACR AUTO SECURITY REVIEW
12/13/2001	19	IEXX	INITIAL EXAM TEAM NN

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Status Inquiry
FILING ACKNOWLEDGMENT

Mailing Date:	June 22, 2005	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	Rodney A. Perkins		
Title:	Methods, Systems, and Kits for Lung Volume Reduction		

Please stamp the date of receipt of the enclosed documents and return this card to addressee

✓
- ✓ -
- -

9 pgs Status Inquiry w/copy of previously submitted Amendment
1 Return Postcard
10 pages

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

PATENT
Attorney Docket No.: 017534-000730US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450 On June 22, 2005

TOWNSEND and TOWNSEND and CREW LLP

By: JoAnn Evangelista
JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND
KITS FOR LUNG VOLUME
REDUCTION

Customer No.: 20350

Confirmation No. 7372

Examiner: THOMPSON, Kathryn L.

Technology Center/Art Unit: 3763

STATUS INQUIRY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants request to be informed of the status of the above-referenced application. A response to an Office Action was mailed on August 20, 2004, a copy of which is attached. A return postcard shows the response was received.

Review of PAIR on June 11, 2005, shows that an Amendment was received on August 24, 2004, but the next entry shows that the file was "marked lost" on February 10, 2005.

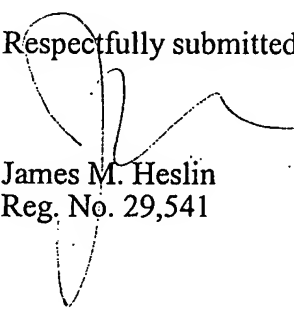
PATENT

Attorney Docket No.: 017534-000730US

Nothing has been received from the Patent Office concerning this application since the Office Action mailed on February 23, 2004.

Clarification is requested.

Respectfully submitted,



James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 650-326-2400 / Fax: 415-576-0300
Attachments: *Office Action mailed 08/20/2004*
JMH:jke /

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE/
AMENDMENT w/Extension of Time (3 mo)
FILING ACKNOWLEDGMENT**

Mailing Date:	August 20, 2004	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

Please stamp the date of receipt of the enclosed documents and return this card to addressee:

- √- 1 pg Transmittal
- √- 2 pgs Fee Transmittal (duplicate)
- √- 1 pg Extension of Time
- √- 3 pgs Amendment
- √- 1 Return Postcard
- 8 pages

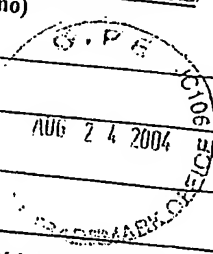
COPY

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE/
AMENDMENT w/Extension of Time (3 mo)
FILING ACKNOWLEDGMENT**


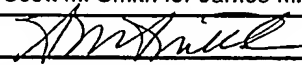
Mailing Date:	August 20, 2004	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

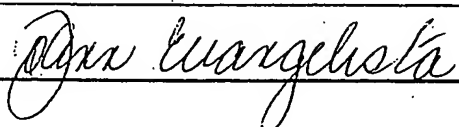
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- √- 1 pg Extension of Time
- √- 3 pgs Amendment
- √- 1 Return Postcard
- 8 pages



TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>		Application Number	10/017,068
		Filing Date	December 13, 2001
		First Named Inventor	PERKINS, RODNEY A.
		Art Unit	3763
		Examiner Name	THOMPSON, Kathryn L.
Total Number of Pages in This Submission	8	Attorney Docket Number	017534-000730US

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Technology Center (TC) <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Return Postcard
Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.		
		
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT		
Firm or Individual name	Townsend and Townsend and Crew LLP Scott M. Smith for James M. Heslin Reg. No. 48,268 and Reg. 29,541	
Signature		
Date	August 20, 2004	

CERTIFICATE OF TRANSMISSION/MAILING			
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.			
Typed or printed name	JoAnn Evangelista		
Signature		Date	August 20, 2004

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 475

Complete if Known

Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Examiner Name	THOMPSON, Kathryn L.
Art Unit	3763
Attorney Docket No.	017534-000730US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None
☒ Deposit Account:Deposit
Account
Number

20-1430

Deposit
Account
Name

Townsend and Townsend and Crew LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims		Extra Claims		Fee from below		Fee Paid
Independent Claims						
Multiple Dependent						

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	475
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	200	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3)

(\$) 475

SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	Scott M. Smith for James M. Heslin	Registration No. (Attorney/Agent)	48,268 29,541	Telephone	650-326-2400
Signature				Date	August 20, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and without.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 017534-000730US	
In re Application of RODNEY A. PERKINS et al.			
Application Number 10/017,068		Filed December 13, 2001	
For METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION			
Art Unit 3763		Examiner THOMPSON, Kathryn L.	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

<input type="checkbox"/> One month (37 CFR 1.17(a)(1))	\$
<input type="checkbox"/> Two months (37 CFR 1.17(a)(2))	\$
<input checked="" type="checkbox"/> Three months (37 CFR 1.17(a)(3))	\$950
<input type="checkbox"/> Four months (37 CFR 1.17(a)(4))	\$
<input type="checkbox"/> Five months (37 CFR 1.17(a)(5))	\$

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 475 .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

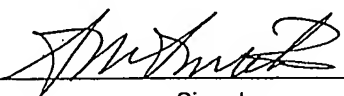
☒ attorney or agent of record.. Registration Number 48,268

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a). _____

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

August 20, 2004

Date



Signature

Scott M. Smith, Reg. No. 48,268
for James M. Heslin, Reg. No. 29,541

Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

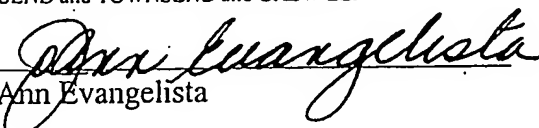
PATENT
Attorney Docket No.: 017534-000730US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On August 20, 2004

TOWNSEND and TOWNSEND and CREW LLP

By:


JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND
KITS FOR LUNG VOLUME
REDUCTION

Customer No.: 20350

Confirmation No. 7372

Examiner: THOMPSON, Kathryn L.

Technology Center/Art Unit: 3763

AMENDMENT

COPY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed February 23, 2004, please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-2 (cancelled).

3. (Currently Amended) A method for lung volume reduction, said method comprising:

isolating a lung tissue segment;

insufflating ~~aspirating~~ the isolated segment with an oxygen-rich gas to cause the segment to collapse by absorption atelectasis; and

sealing an air passage which opens to the lung segment to inhibit reinflation of the segment.

4. (Original) The method of claim 3, wherein sealing comprises deploying a plug in the air passage.

5. (Original) The method of claim 4, wherein deploying comprises advancing the plug through a catheter to the air passage.

6. (New) A method as in claim 3, wherein the gas is at least 50% oxygen by volume.

7. (New) A method as in claim 6, wherein the gas is at least 75% oxygen by volume.

Appl. No. 10/017,068
Amdt. dated August 20, 2004
Reply to Office Action of February 23, 2004

PATENT

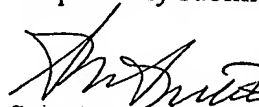
REMARKS/ARGUMENTS

Claims 1-5 were pending. All claims were rejected as being anticipated by U.S. Patent No. 5,957,919 to Laufer. While Applicants do not agree with the rejection, in order to expedite prosecution of the subject application, Applicants have cancelled claims 1 and 2 and amended independent claim 3 to be specifically directed at the protocol described in paragraph 19 in the application. As Laufer nowhere suggests the use of absorption atelectasis for collapsing a lung, Applicants believe that the claims as amended are in condition for allowance.

Applicants intend to file the present claims in a continuation of the present application.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,


Scott M. Smith
Reg. No. 48,268

COPY

For: James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
JMH:jke
60286833 v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE/
AMENDMENT w/Extension of Time (3 mo)
FILING ACKNOWLEDGMENT

Mailing Date:	August 20, 2004	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

Please stamp the date of receipt of the enclosed documents and return this card to addressee:

☒ 1 pg Transmittal
☒ 2 pgs Fee Transmittal (duplicate)
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8 pages

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE/
AMENDMENT w/Extension of Time (3 mo)
FILING ACKNOWLEDGMENT

Mailing Date:	August 20, 2004	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

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☒ 2 pgs Fee Transmittal (duplicate)
☒ 1 pg Extension of Time
☒ 3 pgs Amendment
☒ 1 Return Postcard
8 pages

TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	10/017,068
	Filing Date	December 13, 2001
	First Named Inventor	PERKINS, RODNEY A.
	Art Unit	3763
	Examiner Name	THOMPSON, Kathryn L.
Total Number of Pages in This Submission	8	Attorney Docket Number
		017534-000730US

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation <input type="checkbox"/> Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Technology Center (TC) <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Return Postcard
Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.		
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT		
Firm or Individual name	Townsend and Townsend and Crew LLP	
	Scott M. Smith for James M. Heslin	Reg. No. 48,268 and Reg. 29,541
Signature		
Date	August 20, 2004	

CERTIFICATE OF TRANSMISSION/MAILING			
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Typed or printed name	JoAnn Evangelista		
Signature		Date	August 20, 2004

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 475

Complete if Known

Application Number 10/017,068
 Filing Date December 13, 2001
 First Named Inventor PERKINS, RODNEY A.
 Examiner Name THOMPSON, Kathryn L.
 Art Unit 3763
 Attorney Docket No. 017534-000730US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None
☒ Deposit Account:Deposit
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Number

20-1430

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The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1)

(\$)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims		Extra Claims		Fee from below		Fee Paid
Independent Claims		**	=		X	
Multiple Dependent		**	=		X	

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2)

(\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	475
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

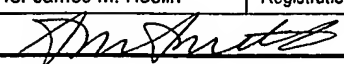
Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3)

(\$)475

SUBMITTED BY

Complete (if applicable)

Name (Print/Type) Scott M. Smith
 for James M. Heslin
 Registration No. (Attorney/Agent) 48,268
 29,541
 Telephone 650-326-2400
 Signature  Date August 20, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 017534-000730US
In re Application of RODNEY A. PERKINS et al.		
Application Number 10/017,068		Filed December 13, 2001
For METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		
Art Unit 3763		Examiner THOMPSON, Kathryn L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

<input type="checkbox"/> One month (37 CFR 1.17(a)(1))	\$
<input type="checkbox"/> Two months (37 CFR 1.17(a)(2))	\$
<input checked="" type="checkbox"/> Three months (37 CFR 1.17(a)(3))	\$950
<input type="checkbox"/> Four months (37 CFR 1.17(a)(4))	\$
<input type="checkbox"/> Five months (37 CFR 1.17(a)(5))	\$

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 475 .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

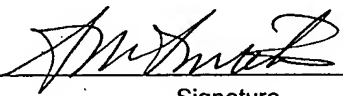
☒ attorney or agent of record.. Registration Number 48,268

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a). _____

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August 20, 2004

Date



Signature

Scott M. Smith, Reg. No. 48,268
for James M. Heslin, Reg. No. 29,541

Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

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PATENT
Attorney Docket No.: 017534-000730US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On August 20, 2004

TOWNSEND and TOWNSEND and CREW LLP

By:


JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND
KITS FOR LUNG VOLUME
REDUCTION

Customer No.: 20350

Confirmation No. 7372

Examiner: THOMPSON, Kathryn L.

Technology Center/Art Unit: 3763

AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed February 23, 2004, please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-2 (cancelled).

3. (Currently Amended) A method for lung volume reduction, said method comprising:

isolating a lung tissue segment;

insufflating ~~aspirating~~ the isolated segment with an oxygen-rich gas to cause the segment to collapse by absorption atelectasis; and

sealing an air passage which opens to the lung segment to inhibit reinflation of the segment.

4. (Original) The method of claim 3, wherein sealing comprises deploying a plug in the air passage.

5. (Original) The method of claim 4, wherein deploying comprises advancing the plug through a catheter to the air passage.

6. (New) A method as in claim 3, wherein the gas is at least 50% oxygen by volume.

7. (New) A method as in claim 6, wherein the gas is at least 75% oxygen by volume.

Appl. No. 10/017,068
Amdt. dated August 20, 2004
Reply to Office Action of February 23, 2004

PATENT

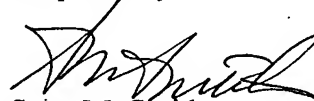
REMARKS/ARGUMENTS

Claims 1-5 were pending. All claims were rejected as being anticipated by U.S. Patent No. 5,957,919 to Laufer. While Applicants do not agree with the rejection, in order to expedite prosecution of the subject application, Applicants have cancelled claims 1 and 2 and amended independent claim 3 to be specifically directed at the protocol described in paragraph 19 in the application. As Laufer nowhere suggests the use of absorption atelectasis for collapsing a lung, Applicants believe that the claims as amended are in condition for allowance.

Applicants intend to file the present claims in a continuation of the present application.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Scott M. Smith
Reg. No. 48,268

For: James M. Heslin
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TOWNSEND *and* TOWNSEND *and* CREW LLP



US005957919A

United States Patent [19]
Laufer[11] **Patent Number:** **5,957,919**
[45] **Date of Patent:** **Sep. 28, 1999**[54] **BLEB REDUCER**[76] **Inventor:** Michael D. Laufer, 1259 El Camino
Real, #211, Menlo Park, Calif. 94025[21] **Appl. No.:** 08/887,206[22] **Filed:** Jul. 2, 1997[51] **Int. Cl.⁶** A61B 17/38[52] **U.S. Cl.** 606/28; 606/27[58] **Field of Search** 606/28, 14, 13,
606/40, 41, 42, 46, 48, 49, 27; 607/96,
98, 99, 100, 102, 122, 126, 128; 128/397[56] **References Cited****U.S. PATENT DOCUMENTS**

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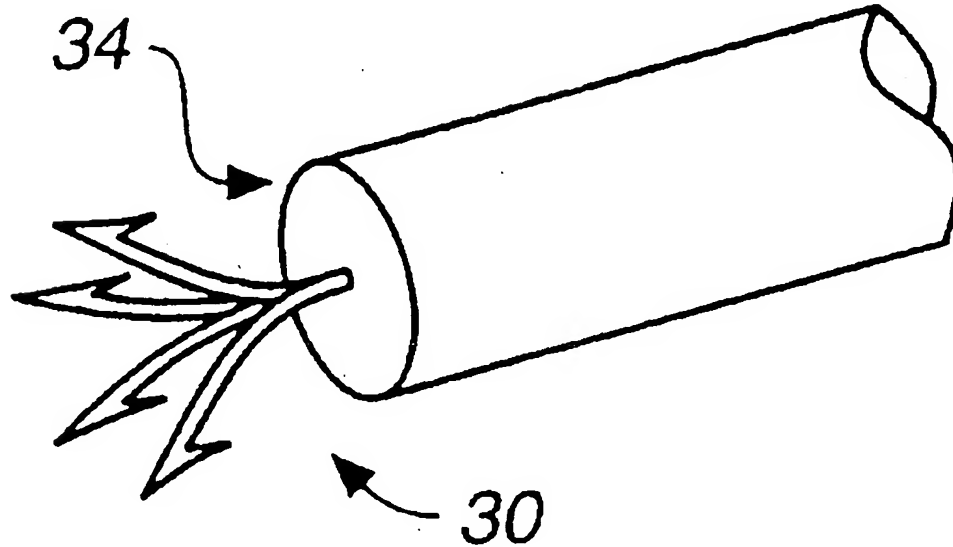
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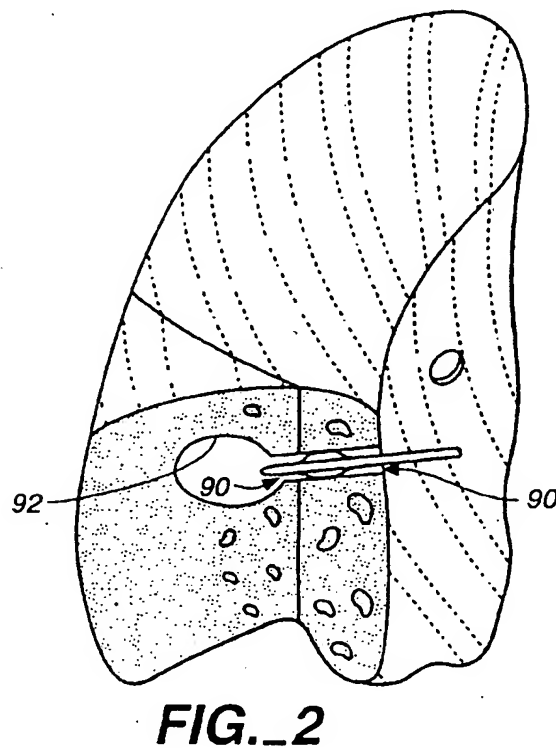
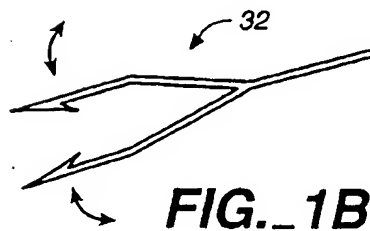
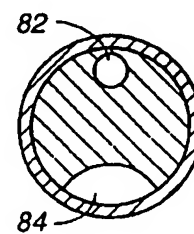
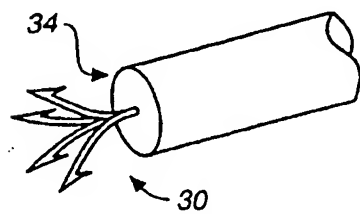
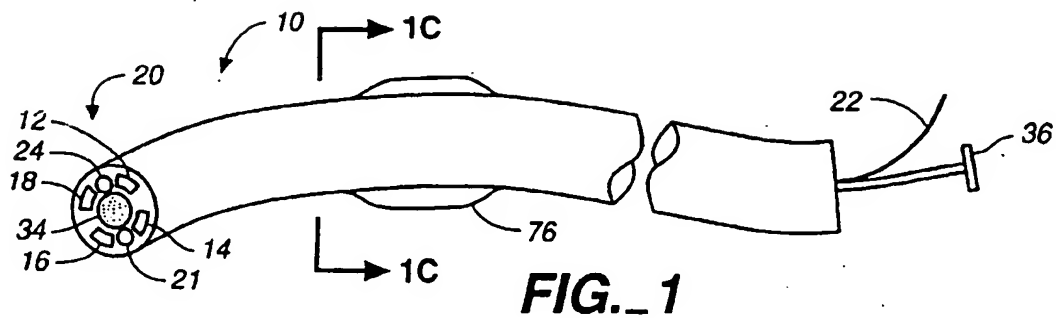
Primary Examiner—Michael Buiz**Assistant Examiner**—Julian W. Woo**Attorney, Agent, or Firm**—Burns, Doane, Swecker &
Mathis, LLP

[57]

ABSTRACT

A device and method for treating hollow, elastic body structures such as blebs in lungs are provided. The device includes an elongated member having a heating element that comprises one or more energy delivery members. The method includes heating said body structure to cause at least a portion of the cross links of the collagen in the wall to unlink/open and subsequently form new cross links after the diameter of said body structure has been significantly reduced and collagen fibers have realigned.

58 Claims, 2 Drawing Sheets



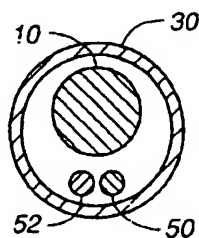
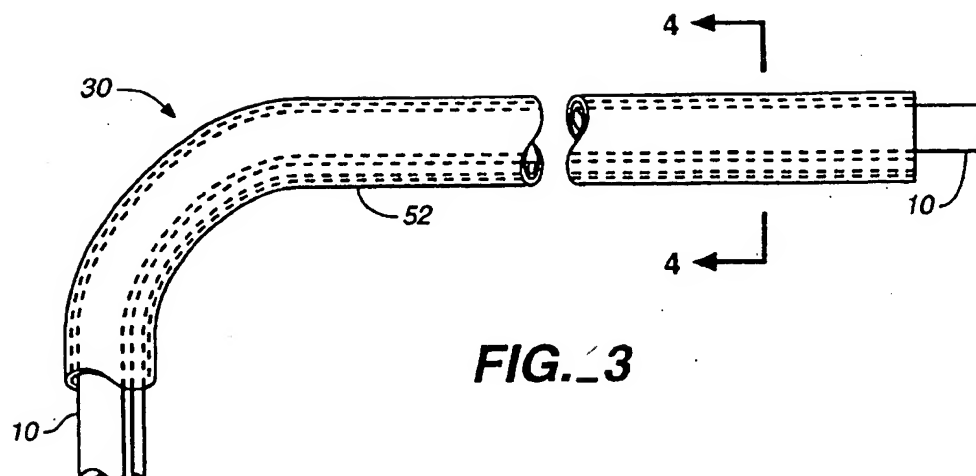


FIG. 4

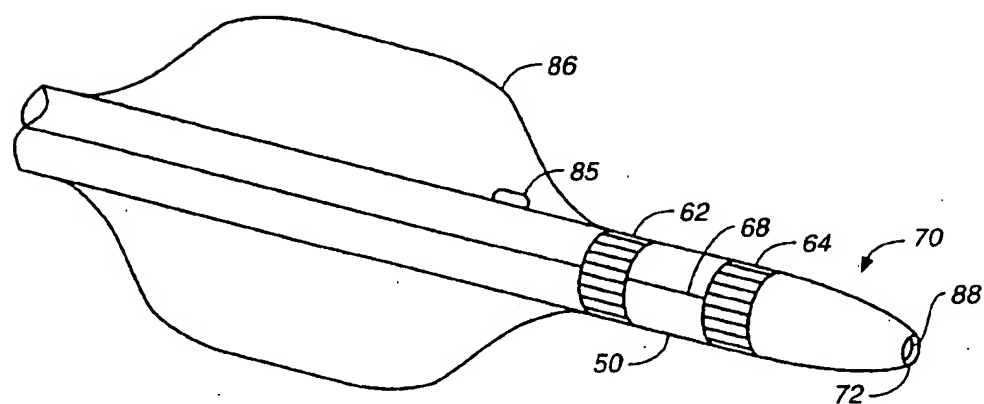


FIG. 5

BLEB REDUCER

FIELD OF THE INVENTION

The present invention relates to a device and method for treatment of hollow, elastic body structures and more particularly for treatment of blebs in the lungs.

BACKGROUND OF THE INVENTION

Blebs are abnormal vacuoles in the lungs which may range from about 3 mm to several centimeters in size. Blebs often develop when alveolar walls deteriorate thereby transforming a mass of individual alveoli into one or more blebs. The alveoli are small, polyhedral recesses composed of a fibrillated connective tissue and surrounded by a few involuntary muscular and elastic fibers. As is apparent, the presence of blebs adversely affects the respiratory function of the lungs by inducing the surface area available for actual gaseous exchange in respiration. For severe cases, surgeons have endeavored to alleviate the disabling conditions associated with blebs by removing portions of lungs containing blebs. These operations are quite risky and are considered final options.

Notwithstanding the conventional treatments available, there exists a need in the art for an effective treatment for conditions associated with blebs and other hollow, elastic body structures. Specifically, there is a need for effective treatment which only requires minimal surgery.

SUMMARY OF THE INVENTION

The present invention is based in part on the discovery that the size of a bleb can be significantly reduced by subjecting the surface of the bleb to a sufficient amount of heat to cause at least a portion of the crosslinks of the collagen fibers to open and subsequently form new cross links after the collagen fibers have realigned.

In one aspect, the invention is directed to an apparatus for treating hollow, elastic body structures such as blebs in the lungs which includes a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes collagen in the wall of said structure to undergo a structural transformation effective to reduce the size of said structure, a means for attaching the treatment device to a surface of said structure, and a source of energy that is conducted to the heating element.

In another aspect, the invention is directed to an apparatus for treating a bleb which defines a cavity which includes a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes collagen in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen, a source of energy that is conducted to the heating element, and means for removing air from the cavity.

The invention is further directed to methods of treating and removing hollow, elastic body structure such as a bleb. One method includes the procedure of heating the wall of said structure with sufficient energy to cause the collagen in the wall to undergo a structural transformation which effectively reduces the size of said structure. Another method includes the procedure of removing air from the cavity of said structure to reduce the size of the cavity. This procedure effectively reduces the size of said structure. Furthermore, the method may include heating and sealing the air passage

(s) or channel(s) leading to the cavity and thereby fix the size of a bleb. In one application the bronchiole leading to the bleb is heated to seal the bronchiole lumen thereby preventing the bleb from redeveloping.

BRIEF DESCRIPTION OF THE DRAWINGS

As used herein, like reference numerals will designate similar elements in the various embodiments of the present invention wherein:

FIGS. 1, 1A, 1B and 1C illustrate an embodiment of the treatment apparatus;

FIG. 2 illustrates implementation of the treatment apparatus through a partially exposed and enlarged section of lung tissue;

FIGS. 3 and 4 illustrate a bronchoscope; and

FIG. 5 illustrates an embodiment of the treatment apparatus.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to devices and methods for treating hollow, elastic body structures that are typically abnormal manifestations. These structures have cavities whose walls contain collagen. As further described herein the collagen will respond to heat treatment thereby reducing the size of the cavities. Prior to treatment, these cavities may range from about 3 mm to several centimeters in size. The invention is particularly suited for treating blebs in the lungs. The invention will be described using the treatment of blebs as the illustrative example, however, it is understood that the invention is applicable generally to the treatment of hollow, elastic body structures.

FIG. 1 illustrates an embodiment of the inventive treatment apparatus which includes an elongated, cylindrical member 10 having a heating element that has a plurality of electrodes designated 12, 14, 16 and 18, each having an exposed distal end which may be substantially flush with the surface of the distal end 20 of the member. The electrodes are electrically connected to a source of RF energy via connector 22. Preferably the exposed surface of the electrodes collectively has a surface area of about 10 mm² to about 100 cm². The treatment apparatus has an outer diameter that is small enough to enter a bleb or can be expanded to fill the bleb or can be expanded to fill the bleb as further described herein. Typically, the outer diameter ranges from about 2 French to about 8 French prior to any expansion.

The function of the heating element is to apply a sufficient amount of energy to the walls of a bleb to cause collagen to undergo a structural transformation to cause the walls to shrink. In this embodiment, energy emanates from the exposed distal ends from the electrodes so that following treatment with this particular apparatus, the size of the bleb is significantly reduced or the bleb is eliminated altogether. As is apparent, the number and surface area of each electrode are not critical. In the case where the surface area is small relative to the diameter of the bleb, it may be necessary to move the apparatus and heat more than one area of the wall in order to transform sufficient amounts of the collagen to reduce the size of the bleb and to distribute the heat more uniformly.

The heating element is made of any suitable biocompatible material such as, for example, conductive polymer, stainless steel, platinum, other noble metals, or shape memory alloy, such as nickel-titanium-alloy (NitinolTM) commercially available from Raychem Corporation, Menlo

Park, Calif.). Member 10 is made of a flexible material so that it can be maneuvered through a catheter or bronchoscope as described herein. The term "catheter" refers generally to a tubular device suitable for insertion into the a bleb through the bronchioles. A bronchoscope is a modified catheter which is an illuminating instrument for inspecting and passing instruments (e.g., treatment device) into the bronchioles.

When the treatment apparatus is positioned at the treatment site, an RF generator is activated to provide suitable RF energy, preferably at a selected frequency in the range of 10 MHz to 1000 MHz. The emitted energy is converted within the tissue into heat in the range of about 40° C. to about 95° C. As the temperature increases, it is believed that the collagen undergoes a structural transformation whereby the collagen fibers contract and new cross links are formed.

RF energy is no longer applied after there has been sufficient transformation, e.g., shrinkage, of the collagen fibers which may be gauged by removing the heating device from the treatment site and conducting a visual inspection. Sufficient shrinkage may also be detected by fluoroscopy, external ultrasound scanning, pulse-echo ultrasound scanning, sensing the collapsing or straightening of the heating element with appropriate feedback variables, impedance monitoring or any other suitable method for pulmonary function testing.

Substantial transformation may be achieved very rapidly, depending upon the specific treatment conditions. Because the transformation can proceed at a rather rapid rate, the RF energy should be applied at low power levels. Preferably, the RF energy is applied for a length of time in the range of about 1 second to about 120 seconds. Suitable RF power sources are commercially available and well known to those skilled in the art. In one embodiment the RF generator employed has a single channel, delivering approximately 1 to 10 watts of RF energy and possessing continuous flow capability. The rate of transformation can be controlled by varying the energy delivered to the heating element.

Besides using RF energy for energizing the heating element, it is to be understood that other forms of energy such as alternating current, microwaves, ultrasound, and light either coherent (e.g., laser) or incoherent (e.g., light emitting diode or tungsten filament) can be used, and that the thermal energy generated from a resistive coil, a hot fluid element (e.g., circulating liquids, gases, combinations of liquids and gases, etc.), a curie point element, or similar elements can be used as well. The hot fluid element may comprise, for example, an elongated member similar to the one illustrated in FIG. 1 that includes a conduit system whereby heated fluid is transported through the member and then channeled outward toward the surface of the distal end 20 of the member. Regardless of the source, the energy delivered to the bleb wall should not ablate the tissue.

The heating element, as shown in FIG. 1, operates as a unipolar, internal electrode in the patient's body. An outer electrode (not shown) having a much larger surface area than that of the electrode bands is placed on the outer surface of the patient's body. For example, an external metal mesh or solid plate is placed on the skin. Both electrodes are connected to an RF generator which produces an electric field at a high frequency within the patient's body. Because the collective surface area of the electrode bands is much smaller than that of the outer electrode, the density of the high frequency electric field is much higher around the electrode bands. The electric field reaches its highest density between the two electrodes in the region near the heating

element. The increased density of the field around the distal ends of the electrodes produces localized heating of the tissue of the bleb wall.

A heating element comprising a bipolar electrode can also be used. Referring to FIG. 1, in such a bipolar electrode arrangement, electrodes 12 and 16 can be connected to the positive electrode of the RF generator and electrodes 14 and 18 are connected to the negative electrode. The material between the conductive elements are electrically insulated. In this case, FIG. 1 illustrates a heating element having multiple, i.e., double, bipolar electrodes. The electrodes emit RF energy with the first conductive element acting as the active electrode and the second conductive element acting as the return electrode, or vice versa.

The treatment apparatus preferably includes a device for attaching the apparatus to the bleb wall. FIG. 1A illustrates one device which comprises a plurality of generally axially extending hooks 30 that are made of metal or other suitable material. FIG. 1B illustrates another device which comprises expandable prongs 32. The hook and prong devices are sized to be received with lumen 24 of the treatment apparatus.

The treatment apparatus can be maneuvered to a particular bleb initially through the bronchus, which upon entering the substance of the lung, divides and subdivides bipinnately, throughout the entire organ. Sometimes multiple branches arise together, and occasionally small lateral branches are given off from the sides of a main trunk. Each of the smaller subdivisions of the bronchi enters a pulmonary lobule, and is termed a lobular bronchial tube or bronchiole. The bronchiole becomes enlarged, and is termed the atrium or alveolar passage; from it are given off, on all sides, ramifications, called infundibula, which are closely beset in all directions by alveoli.

In operation, after the treatment apparatus is maneuvered to the bleb surface through the bronchiole, the hooks or prongs are projected from lumen 24 when the surgeon engages (e.g., presses) actuator 36 which is connected to the hooks or prongs via a stiff wire. The hooks or prongs are then manipulated to fasten onto tissue on the bleb surface whereupon the actuator is disengaged and the hooks or prongs are retracted. In this fashion, the bleb tissue becomes attached to the treatment apparatus and as a corollary the heating element becomes positioned adjacent to (or is in physical contact with) the bleb surface.

The treatment apparatus may further include an inflatable balloon device 76 which is made of a flexible, expandable material. As shown in FIG. 1C, the apparatus includes at least two internal passageways 82 and 84. For example, passageway 82 may be in communication with lumen 24 and passageway 84 may be in communication with the balloon device.

In operation, as illustrated in FIG. 2, after the treatment apparatus is inserted into the bronchiole 90 which leads to bleb 92, the balloon device is inflated with air or other suitable fluid so that the outer surface of the balloon is in physical contact with the inner surface of the bronchiole. Next the air is withdrawn from the bleb through lumen 24 and via passageway 84 which in turn is connected to an aspirator device (not shown). The suction will cause the size of the bleb to decrease. Once the size of the bleb has been reduced sufficiently so as to be in contact with the distal ends of the electrodes, the heating elements can be energized to complete the treatment process. The treatment apparatus may include a conventional pressure sensing gauge 21 to measure the pressure in the cavity of the bleb.

The segment of the treatment apparatus forming the balloon is fabricated of material that is expandable and

scanning, pulse-echo ultrasound scanning, sensing the collapsing or straightening of the heating element with appropriate feedback variables, impedance monitoring or any other suitable method.

Besides using RF energy for energizing the heating element, it is to be understood that other forms of energy such as those described for the device of FIG. 1 including alternating current, microwaves, ultrasound, and light either coherent (e.g., laser) or incoherent (e.g., light emitting diode or tungsten filament) can be used, and that the thermal energy generated from a resistive coil, a hot fluid element (e.g., circulating liquids, gases, combinations of liquids and gases, etc.) can be used as well.

The heating element, as shown in FIG. 5 operates as a unipolar, internal electrode in the patient's body. An outer electrode (not shown) having a much larger surface area than that of the electrode bands is placed on the outer surface of the patient's body. A heating element comprising a bipolar electrode can also be used.

While the heating elements have been shown as electrode bands, other configurations can be used such as, for example, spiral, ring and grid patterns. These elements will create corresponding patterns on the lumen wall. One limitation is that the heating elements have sufficient surface area in contact with the wall of the lumen so that the heat treatment process can be completed within a reasonable time.

The invention is also directed to the demonstration or instruction of the inventive surgical techniques including, but not limited to, actual instructions involving patients, audio-visual presentations, animal demonstrations, and the like.

While several particular embodiments of the invention have been illustrated and described, it will be apparent that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. An apparatus for treating an elastic body structure that defines a cavity which comprises:

a treatment device comprising an elongated member and a non-tissue penetrating heating element that comprises one or more energy delivery members which when energized causes tissue in the wall of the cavity to undergo a structural transformation effective to reduce the size of the cavity;

non-energy delivering means for attaching the treatment device to a surface of the cavity with the non-tissue penetrating heat element abutting walls of the cavity; and

a source of energy that is conducted to the heating element.

2. The apparatus of claim 1 wherein the source of energy produces energy in a form that is selected from the group consisting of RF energy, alternating current, microwaves, ultrasound, coherent light, incoherent light, thermal energy, and mixtures thereof.

3. The apparatus of claim 2 wherein the one or more energy delivery members each comprise an electrode and wherein a segment of the elongated member comprises elastic material and wherein each electrode has a distal portion that is positioned on an outer surface of the segment.

4. An apparatus for treating an elastic body structure that defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy

delivery members which when energized causes tissue in the wall of the cavity to undergo a structural transformation effective to reduce the size of the cavity;

means for attaching the treatment device to a surface of the cavity; and

a source of energy that is conducted to the heating element, wherein the one or more energy delivery members comprise one or more sets of double electrode bands wherein each set comprises a first electrode which is connected to the positive electrode of an RF generator and a second electrode which is connected to the negative electrode of the RF generator.

5. The apparatus of claim 1 wherein the one or more energy delivery members emit light energy.

6. The apparatus of claim 1 wherein the one or more energy delivery members comprise a conduit that channels heated fluid into and out of the elongated member.

7. The apparatus of claim 1 wherein the source of energy comprises a radio frequency generator.

8. The apparatus of claim 1 further comprising a feedback indicator.

9. The apparatus of claim 8 wherein the feedback indicator is an auditory signal.

10. The apparatus of claim 8 wherein the feedback indicator is a visual signal.

11. The apparatus of claim 8 wherein the feedback indicator is indicative of tissue shrinkage.

12. The apparatus of claim 8 wherein the feedback indicator is indicative of temperature.

13. The apparatus of claim 8 wherein the feedback indicator is indicative of electrical characteristics.

14. The apparatus of claim 8 wherein the feedback indicator is indicative of pressure within the cavity.

15. The apparatus of claim 1 wherein the means for attaching the treatment device comprises hooks or prongs.

16. The apparatus of claim 1 wherein the treatment device has a tubular member on an outer surface of the elongated member and wherein the elongated member defines a first diameter and the tubular member having a second, expanded and deformed diameter upon an application of a radially, outwardly extending force.

17. The apparatus of claim 1 wherein the heating elements further comprise one or more electrode bands that are each spaced apart from an adjacent band.

18. The apparatus of claim 1 wherein the treatment device comprises means for removing air from the cavity.

19. The apparatus of claim 18 wherein the means for removing air comprises a lumen in the treatment device that is in communication with an aspirator.

20. An apparatus for treating an elastic body structure that defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue

in the wall of the cavity to undergo a structural transformation effective to reduce the size of the cavity;

means for attaching the treatment device to a surface of the cavity; and

a source of energy that is conducted to the heating element wherein the treatment device includes a lumen for removing air from the cavity and the heating element is located on an inner surface of the lumen.

21. An apparatus for treating a bleb which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue

in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen;

a source of energy that is conducted to the heating element;

an inflatable balloon positioned on the elongated member for sealing the bronchiole and preventing air from passing into the bleb; and

means for removing air from the bleb.

22. The apparatus of claim 21 wherein the one or more energy delivery members each comprises an electrode band.

23. The apparatus of claim 22 wherein each electrode is positioned on an outer surface of the inflatable balloon.

24. The apparatus of claim 21 wherein the one or more energy delivery members comprise one or more sets of double electrode bands wherein each set comprises a first electrode which is connected to the positive electrode of an RF generator and a second electrode which is connected to the negative electrode of the RF generator.

25. An apparatus for treating a bleb which defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen;

a source of energy that is conducted to the heating element;

means for removing air from the cavity; and

wherein the one or more energy delivery members emit light energy.

26. An apparatus for treating a bleb which defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen;

a source of energy that is conducted to the heating element;

means for removing air from the cavity; and

wherein the one or more energy delivery members comprise a conduit that channels heated fluid into and out of the elongated member.

27. The apparatus of claim 21 wherein the source of energy comprises a radio frequency generator.

28. The apparatus of claim 21 further comprising a feedback indicator.

29. The apparatus of claim 28 wherein the feedback indicator is an auditory signal.

30. The apparatus of claim 28 wherein the feedback indicator is a visual signal.

31. The apparatus of claim 28 wherein the feedback indicator is indicative of shrinkage.

32. The apparatus of claim 28 wherein the feedback indicator is indicative of temperature.

33. The apparatus of claim 28 wherein the feedback indicator is indicative of electrical characteristics.

34. The apparatus of claim 21 further comprising means for attaching the treatment device to the bleb comprising hooks or prongs.

35. An apparatus for treating a bleb which defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen;

a source of energy that is conducted to the heating element;

means for removing air from the cavity; and

wherein the treatment device has a tubular member on an outer surface of the elongated member wherein the elongated member defines a first diameter and the tubular member having a second, expanded and deformed diameter upon an application of a radially, outwardly extending force, which second diameter is variable and dependent upon the amount of force applied to the tubular member.

36. The apparatus of claim 35 wherein the means for removing air comprises a lumen in the treatment device that is in communication with aspirator.

37. The apparatus of claim 36 wherein the heating element is located on an inner surface of the lumen.

38. A method of treating a bleb in a lung that defines a cavity that comprises the step of:

heating a wall surface of said bleb to a temperature effective to cause tissue in the wall of the cavity to undergo a structural transformation to reduce the size of the cavity.

39. The method of claim 38 wherein the wall of the cavity is heated to a temperature in the range between about 40° C. and about 95° C.

40. The method of claim 39 wherein the wall is heated for about 1 to about 120 seconds.

41. The method of claim 38 wherein the step of heating the surface comprises:

advancing a treatment apparatus into said structure of the individual; and

energizing the treatment apparatus to raise the temperature of the surface to sufficiently affect collagen in the wall of the cavity to undergo a structural transformation.

42. The method of claim 41 wherein the treatment apparatus comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes collagen in the wall of said structure to undergo a structural transformation effective to reduce the size of the cavity;

means for attaching the treatment device to a surface of said structure; and

a source of energy that is conducted to the heating element.

43. A method of treating a bleb which defines a cavity in the lung of an individual that comprises the steps of:

removing air from the cavity through a bronchiole that is in communication with the cavity to cause a reduction in size of the cavity; and

heating the wall of the bronchiole to seal the bronchiole lumen.

44. The method of claim 43 wherein the wall of the bronchiole is heated to a temperature in the range between about 40° C. and about 95° C.

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45. The method of claim 44 wherein the wall of the bronchiole is heated for about 1 to about 120 seconds.

46. The method of claim 43 wherein the step of heating the wall of the bronchiole comprises:

advancing a treatment apparatus into a lumen of the bronchiole;

energizing the treatment apparatus to raise the temperature of the surface of the wall to sufficiently affect collagen in the wall to undergo a structural transformation.

47. The method of claim 46 wherein the treatment apparatus comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes collagen in the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and seal the bronchiole;

a source of energy that is conducted to the heating element; and

means for removing air from the cavity.

48. A method of treating a bleb which defines a cavity in the lung of an individual that comprises the steps of:

drawing air from the cavity to cause a reduction in size of the cavity; and

heating a surface of the bleb wall to seal the cavity.

49. The method of claim 48 wherein the step of drawing air from the cavity causes the wall of the bleb to invaginate.

50. The method of claim 49 wherein heating the surface of the bleb wall fixes the size of the bleb.

51. The method of claim 48 wherein the wall of the bleb is heated to a temperature in the range between about 40° C. and about 95° C.

52. The method of claim 51 wherein the wall of the bleb is heated for about 1 to about 120 seconds.

53. The method of claim 48 wherein the step of drawing air from the cavity comprises:

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(a) advancing a treatment apparatus into a lumen of the bronchiole that is in communication with the cavity wherein the treatment apparatus comprises:

(i) an elongated member and a heating element that comprises one or more energy delivery members which when energized causes collagen in the bleb wall to undergo a structural transformation effective to reduce the size and seal the bleb;

(ii) a source of energy that is conducted to the heating element; and;

(iii) means for removing air from the cavity; and

(b) activating said means for removing air.

54. The method of claim 53 wherein the means for removing air comprises a lumen in the treatment apparatus that is in communication with an aspirator.

55. The method of claim 54 wherein the heating element is located on an inner surface of the lumen.

56. An apparatus for treating an elastic body structure that defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes tissue in the wall of the cavity to undergo a structural transformation effective to reduce the size of the cavity;

means for attaching the treatment device to a surface of the cavity;

a source of energy that is conducted to the heating element; and

wherein the heating elements further comprise one or more electrode bands that are each spaced apart from an adjacent band.

57. The apparatus of claim 1 wherein the treatment device includes a proximal end and a distal end, and the heating element is positioned proximal of the attaching means.

58. The apparatus of claim 3 wherein the elastic segment of the elongated member is radially expandable.

* * * * *



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,068	12/13/2001	Rodney A. Perkins	017534-000730US	7372

20350 7590 02/23/2004

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EXAMINER

THOMPSON, KATHRYN L

ART UNIT

PAPER NUMBER

3763

DATE MAILED: 02/23/2004

Response Due 5/23/04 53P

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/017,068

Applicant(s)

PERKINS ET AL.

Examiner

Kathryn L. Thompson

Art Unit

3763

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Laufer (US 5,957,919). Laufer discloses a method of reducing lung size of a lung, including the steps of inserting a conduit down a trachea, into a mainstem bronchus, into a bronchial branch, and into a bronchial sub-branch communicating with a lung portion of the lung to be reduced in size (Column 5, Lines 20-27), pulling a vacuum in the lung portion to collapse the lung portion (Column 6, Lines 26-37), and deploying an obstructing member/plug including feeding the obstructing member/plug down the conduit and into the bronchial sub-branch (Column 4, Lines 52-65).

Response to Arguments

Applicant's arguments, see Paper No. 5, filed August 4, 2003, with respect to the rejection(s) of claim(s) 1-5 under Medhkour et al and Medhkour et al in view

Art Unit: 3763

of Dayal have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Laufer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathryn L Thompson whose telephone number is 703-305-3286. The examiner can normally be reached on 8:30 AM - 6:00 PM; 1st Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on 703-308-3552. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KLT



BRIAN L. CASLER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 3700

Notice of References Cited

Application/Control No.

10/017,068

Applicant(s)/Patent Under
Reexamination
PERKINS ET AL.

Examiner

Kathryn L Thompson

Art Unit

3763

Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,957,919	09-1999	Laufer, Michael D.	606/28
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Page 3 of **Complete If Known**

Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A., et. al.
Art Unit	3763
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

U.S. PATENT DOCUMENTS

Examiner	Cite No. ¹	Document Number Number Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
<i>[Signature]</i>	AA	US-5,928,264	07-27-1999	Sugarbaker et al.	
<i>[Signature]</i>	AB	US-5,957,919	09-28-1999	Laufer	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ³
		Country Code ³	Number ⁴ Kind Code ⁵ (if known)				
							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
<i>[Signature]</i>	AC	BOLLIGER et al. "Evaluation of high risk lung resection candidates: pulmonary haemodynamic versus exercise testing. A series of five patients." <i>Respiration</i> (1994) 61(4):181-186	
<i>[Signature]</i>	AD	MELENDEZ et al., (abstract) "Predictive respiratory complication quotient predicts pulmonary complications in thoracic surgical patients" <i>Annals of Thoracic Surgery</i> (12/1998) 66(6):2164.	
<i>[Signature]</i>	AE	McKENNA et al., (abstract) "Patient selection criteria for lung volume reduction surgery" <i>Journal of Thoracic and Cardiovascular Surgery</i> (12/1997) 114(6):957-964.	

60007233 v1

Examiner Signature	<i>[Signature]</i>	Date Considered	02/12/04
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 120 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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60007233 v1

TOWNSEND *and* TOWNSEND *and* CREW LLP

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE/
RESPONSE w/SUPP. IDS
FILING ACKNOWLEDGMENT**

Mailing Date:	August 1, 2003	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

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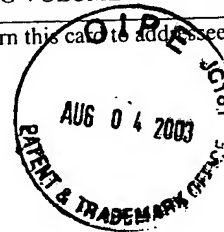
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RESPONSE w/SUPP. IDS
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Mailing Date:	August 1, 2003	Serial No.:	10/017,068
File No.:	017534-000730US	Attorney:	JMH/jke
Applicant:	PERKINS, Rodney A.		
Title:	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		

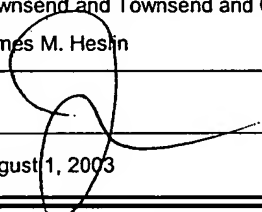
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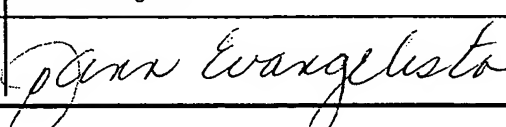
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 11 pages



TRANSMITTAL FORM (to be used for all correspondence after initial filing)		Application Number	10/017,068
		Filing Date	December 13, 2001
		First Named Inventor	PERKINS, RODNEY A.
		Art Unit	3763
		Examiner Name	THOMPSON, Kathryn L.
Total Number of Pages in This Submission	11	Attorney Docket Number	017534-000730US

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Response <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input checked="" type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s)	<input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Return Postcard
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual	Townsend and Townsend and Crew LLP James M. Heslin Reg. No. 29,541
Signature	
Date	August 1, 2003

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$ 645

Complete if Known

Application Number 10/017,068
Filing Date December 13, 2001
First Named Inventor PERKINS, RODNEY A.
Examiner Name THOMPSON, Kathryn L.
Art Unit 3763
Attorney Docket No. 017534-000730US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ MoneyOrder ☐ Other ☐ None

☒ Deposit Account:

Deposit
Account
Number

20-1430

Deposit
Account
Name

Townsend and Townsend and Crew LLP

The Commissioner is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments
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☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity	Small Entity	Fee Code	Fee (\$)	Fee Description	Fee Paid
		1001	750	Utility filing fee	
		1002	330	Design filing fee	
		1003	520	Plant filing fee	
		1004	750	Reissue filing fee	
		1005	160	Provisional filing fee	

SUBTOTAL (1)

(\$)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims	Extra Claims	Fees from below	Fee Paid
Independent Claims			
Multiple Dependent			

Large Entity	Small Entity	Fee Code	Fee (\$)	Fee Description
		1202	18	Claims in excess of 20
		1201	84	Independent claims in excess of 3
		1203	280	Multiple dependent claim, if not paid
		1204	84	** Reissue independent claims over original patent
		1205	18	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2)

(\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large	Entity	Small	Entity	Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	465
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	180
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3)

(\$645

SUBMITTED BY

Complete (if applicable)

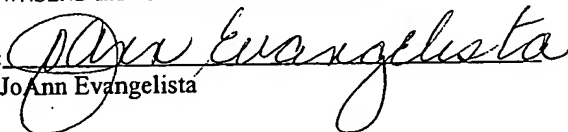
Name (Print/Type) James M. Heslin Registration No. (Attorney/Agent) 29,541 Telephone 650-326-2400
Signature Date August 1, 2003

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PATENT
Attorney Docket No.: 017534-000730US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450 On August 1, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: 
JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION

Customer No.: 20350

Confirmation No.: 7372

Examiner: THOMPSON, Kathryn L.

Technology Center/Art Unit: 3763

RESPONSE

Mail Stop: 3763
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed February 19, 2003, Applicants respectfully request reexamination and reconsideration of the claims in view of the following remarks.

Claims 1-5 are pending. Claims 1, 3, and 4 were rejected as being anticipated by U.S. Patent No. 6,493,589 to Medhkour et al. Claims 2 and 5 were rejected as being obvious over Medhkour in view of Dayal '175. Such rejections are respectfully traversed.

Applicants note that the present application has an effective filing date at least as early as June 28, 2000, since it is continuation of Application No. 09/606,320 filed on that date. With the possible exception of corrections of minor typographical, the Specifications of the

Appl. No. 10/017,068
Response dated August 1, 2003
Reply to Office Action of Feb. 19, 2003

PATENT

present application and of the parent file on June 28, 2000, are identical. Applicants further believe that all pending claims are entitled to priority from the grandparent Application No. 09/347,032, filed on July 2, 1999. For the present, however, Applicants have no need to rely on that date.

U.S. Patent No. 6,493,589 to Medhkour has an actual filing date of August 10, 2000, which is after the effective filing date of the present application. Thus, Applicants believe that the rejections under 35 U.S.C. §102 and 102(e)/103 are improper and request that they be withdrawn.

Applicants realize that the Medhkour '589 patent claims priority from an earlier Continuation-In-Part Application No. 090/304,681, filed on May 4, 1999, now U.S. Patent No. 6,327,505, as well as an even earlier Provisional Patent Application No. 60/084,580, filed on May 7, 1998.

Applicants note, however, that Figs. 15-20 of the cited '589 patent of the cited '589 patent directed particularly at lung treatment were not included in the Parent Application No. 09/304,681 and were added in the application filed on August 10, 2000. Thus, Applicants believe that those portions of the '589 patent which are particularly directed at lung treatments are not available as prior art against the present application.

If the Examiner believes that such teachings are available, it is respectfully requested that the Examiner cite U.S. Patent No. 6,327,505, and provide reasons why the '505 patent would render the present application anticipated and/or obvious.

As an additional matter, Applicants note that certain prior art references are being made of record herein and accompany an IDS. These references were cited in an Office Action in copending related Application Number 09/898,703, which is a divisional of the Parent Application of the present application.

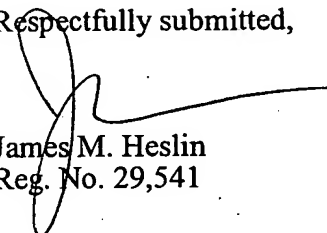
As a final matter, Applicants wish to remind the Examiner, as previously pointed out in the Preliminary Remarks filed together with the application, that claims 1 and 2 herein have been copied from claims 9 and 10 of U.S. Patent No. 6,258,100, which issued on July 10, 2001, from an application filed on October 10, 2000, and which claimed to be a divisional of Application of 09/379,972, filed on August 24, 1999.

Appl. No. 10/017,068
Response dated August 1, 2003
Reply to Office Action of Feb. 19, 2003

PATENT

If for any reason the Examiner believes that a telephone conference would in any way expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 650-326-2400. In response to the Office Action mailed, please enter the following amendments and remarks:

Respectfully submitted,



James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
JMH:jke
60008449 v1

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 017534-000730US
In re Application of RODNEY A. PERKINS et al.		
Application Number 10/017,068		Filed December 13, 2001
For METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION		
Art Unit 3763	Examiner THOMPSON, Kathryn L.	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

<input type="checkbox"/> One month (37 CFR 1.17(a)(1))	\$
<input type="checkbox"/> Two months (37 CFR 1.17(a)(2))	\$
<input checked="" type="checkbox"/> Three months (37 CFR 1.17(a)(3))	\$930
<input type="checkbox"/> Four months (37 CFR 1.17(a)(4))	\$
<input type="checkbox"/> Five months (37 CFR 1.17(a)(5))	\$

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 465 .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record.. Registration Number 29,541

☐ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a). _____

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

August 1, 2003

Date

Signature

James M. Heslin, Reg. No. 29,541

Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below".

☐ *Total of _____ forms are submitted.

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PATENT
Attorney Docket No.: 017534-000730US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450 On August 1, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: JoAnn Evangelista
JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION

Examiner: Kathryn L. Thompson

Art Unit: 3763

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER 37
CFR §1.97 and §1.98

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. Copies of the references are enclosed.

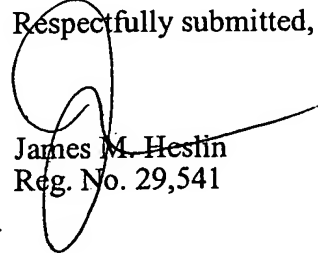
It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR 1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This IDS is being filed before the mailing date of the final Office Action or
Notice of Allowance.

Please charge the IDS fee of \$180 to Deposit Account No. 20-1430. Please
deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,


James M. Heslin
Reg. No. 29,541

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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Page **3**

of

Complete if Known

Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A., et. al.
Art Unit	3763
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

U.S. PATENT DOCUMENTS

Examiner	Cite No. ¹	Document Number Number Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-5,928,264	07-27-1999	Sugarbaker et al.	
	AB	US-5,957,919	09-28-1999	Laufer	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	AC	BOLLIGER et al. "Evaluation of high risk lung resection candidates: pulmonary haemodynamic versus exercise testing. A series of five patients." <i>Respiration</i> (1994) 61(4):181-186	
	AD	MELENDEZ et al., (abstract) "Predictive respiratory complication quotient predicts pulmonary complications in thoracic surgical patients" <i>Annals of Thoracic Surgery</i> (12/1998) 66(6):2164.	
	AE	McKENNA et al., (abstract) "Patient selection criteria for lung volume reduction surgery" <i>Journal of Thoracic and Cardiovascular Surgery</i> (12/1997) 114(6):957-964.	

60007233 v1

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 120 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.
60007233 v1

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^c Department of Radiology, University Hospital, Basel, Switzerland

Evaluation of High-Risk Lung Resection Candidates: Pulmonary Haemodynamics versus Exercise Testing

A Series of Five Patients

Key Words

Pre-operative evaluation
Lung resection
Pulmonary function tests
Pulmonary haemodynamics
Exercise testing
Maximal oxygen uptake

Abstract

We compared the value of exercise testing and measurement of pulmonary haemodynamics (PH) in the pre-operative assessment of 5 patients (mean age: 64 years, 3 men) with clinical stage I or II bronchogenic carcinoma and severe chronic obstructive pulmonary disease. They were considered at high risk due to poor pulmonary function tests (PFT); (one or more of the following): (1) radionuclide calculated postlobectomy FEV₁ <30% predicted, (2) diffusion capacity or transfer factor <60% predicted, combined with a fall in PaO₂ on maximal exercise of >5 mm Hg, (3) a PaCO₂ at rest of >45 mm Hg. Maximal oxygen uptake ($\dot{V}O_{2max}$) during symptom-limited cycle ergometry and PH were measured in these 5 patients. They were considered eligible for lobectomy if they fulfilled at least one of the two criteria: (1) mean pulmonary artery pressure (PAP) of <35 mm Hg and pulmonary vascular resistance of <190 dyn·s·cm⁻⁵ at moderate exercise (40 W), (2) a $\dot{V}O_{2max}$ of ≥ 15 ml/kg/min. Six months postoperatively PFT and $\dot{V}O_{2max}$ were measured again. PAP_{40w} was 21, 38, 38, 46 and 52 mm Hg, respectively, which would have excluded 4/5 patients from surgery. $\dot{V}O_{2max}$ was 21.7, 14.9, 13.4, 19.2 and 18.6 ml/kg/min, respectively, which would have excluded 2/5 patients. Expressed in percent predicted, however, $\dot{V}O_{2max}$ was $\geq 69\%$ in all 5 patients, indicating only mild impairment of exercise capacity in the 2 patients with <15 ml/kg/min $\dot{V}O_{2max}$. Therefore all 5 patients were offered surgery and underwent lobectomy. Apart from 1 prolonged air leak no complications occurred, the mean hospital stay was 16 days (13–21). At 6 months their PFT and $\dot{V}O_{2max}$ were unchanged. In conclusion, in our series of patients with marginal pulmonary function, exercise testing with the determination of $\dot{V}O_{2max}$ was superior to PH measurements for the prediction of operability. It seems that $\dot{V}O_{2max}$ should be expressed as a percent of predicted; however, our findings will need confirmation by future studies with bigger sample sizes.

Received:
October 13, 1993
Accepted after revision:
February 17, 1994

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After written informed consent had been obtained, all 5 patients underwent symptom-limited cycle ergospirometry (cycle: ER 900L, Jaeger; cardiopulmonary stress testing unit: EOS Sprint, Jaeger). Continuous measurements of ventilation, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and pulse rate were averaged every 15 s. Blood pressure was measured manually (Riva-Rocci) every minute. A precordial ECG was monitored continuously (Cardiotest EK 53 R; Hellige, Freiburg, FRG) and hard copies were written at rest, at peak exercise, at the end of the recovery period and additionally when arrhythmias or changes in the ST-T segments occurred. After a 3-min baseline period, the patient started exercising at constant speed on a ramp protocol with a 20 W/min workload increase. The exercise test was stopped when the patients were exhausted, a plateau in $\dot{V}O_2$ uptake appeared or at any signs (ECG) or symptoms of myocardial ischaemia, including a fall in blood pressure. All parameters were recorded until the end of a 6-min recovery period. Arterial blood samples were drawn from the radial or brachial artery at rest and at peak exercise and analysed immediately. Maximal oxygen consumption was measured in millilitres per kilogram per minute and as a percent of predicted according to Jones and Campbell [11]. This prediction equation was chosen as it included sex and age [12, 13]. It further allowed direct comparisons with the studies by Smith et al. [2] and Markos et al. [5] in which $\dot{V}O_{2\max}$ was analysed in absolute as well as in percent of predicted values.

Table 1. Definition of postoperative complications (within 30 days of surgery)

Acute CO ₂ retention (partial pressure of arterial CO ₂ >45 mm Hg)
Prolonged mechanical ventilation (>48 h)
Symptomatic cardiac arrhythmias necessitating treatment
Myocardial infarction
Pneumonia (temperature >38 °C, purulent sputum and infiltrate on chest roentgenogram)
Pulmonary embolism (high-probability ventilation/perfusion scan or diagnostic pulmonary angiogram)
Lobar atelectasis
Death

Table 2. Pre-operative assessment and postoperative course in 5 patients at high risk for postoperative complications

	Patient				
	1	2	3	4	5
Sex	m	f	f	m	m
Age, years	55	66	71	58	70
Height, cm	167	162	163	167	172
Weight, kg	52	69	63	75	71
FVC, litres	3.4	2.9	2.3	2.9	3.0
FVC, % pred.	92	109	88	78	80
FEV ₁ , litres	1.7	1.5	1.1	1.2	1.5
FEV ₁ , % pred.	56	70	53	39	51
FEV ₁ , % ppo	48	65	45	27	49
DL _{co} , % pred.	52	63	72	54	91
K _{co} , % pred.	50	58	67	54	94
ΔPAO ₂ , mm Hg	-20.5	-7.8	3.5	1.8	-2.4
PaCO ₂ rest, mm Hg	38.7	27.9	47.7	49.8	45.3
PaCO ₂ exercise, mm Hg	41.9	31.1	48.7	51.6	57.1
PAP rest, mm Hg	15	15	16	22	25
PAP _{40 w} , mm Hg	21	38	38	46	52
PVR _{40 w} , dyn·s·cm ⁻⁵	42	176	200	161	291
CO rest, l/min	6.3	5.9	4.6	6.6	4.4
CO _{40 w} , l/min	11.7	10	11	13.4	11.6
VO _{2max} , ml/kg/min	21.7	14.9	13.4	19.2	18.6
VO _{2max} , % pred.	81	70	69	76	96
Lobe resected	RUL	RLL	RUL	RLL	LUL
Diagnosis	SCLC	SQ-CA	SQ-CA	SQ-CA	SQ-CA
Tumour stage	I	I	I	II	I
Days in hospital	14	13	21	15	17

FEV₁, % ppo = FEV₁/% postoperative predicted; DL_{co} = diffusion capacity; K_{co} = transfer factor; ΔPAO₂ = difference in PAO₂ at rest - at exercise; PAP_{40 w} = mean pulmonary artery pressure at exercise; PVR_{40 w} = pulmonary vascular resistance at exercise; CO = cardiac output; CO_{40 w} = cardiac output at exercise; RUL = right upper lobe; RLL = right lower lobe; LUL = left upper lobe; SCLC = small-cell lung cancer; SQ-CA = squamous-cell carcinoma.

Measurement of PH

In all 5 high-risk patients right heart catheterization was performed using a Cournand catheter introduced via a precubital vein. Pressure readings at rest and on moderate exercise (40-watt steady-state cycling after 5 min) were obtained in the pulmonary capillary wedge position, the pulmonary artery, the right ventricle and atrium; cardiac output was calculated by the Fick method using the difference in arterial to venous oxygen content and the VO₂.

Criteria of Eligibility for Surgery

According to the PFT results and/or to desaturation on ergospirometry all 5 patients met at least one of the three above-mentioned criteria indicating functional inoperability. They were, however, still considered eligible for lobectomy if they fulfilled at least one of the two criteria: (1) mean PAP of <35 mm Hg combined with a PVR of <190 dyn·s·cm⁻⁵ at moderate exercise (40 W) [14-17] or (2) a VO_{2max} of ≥15 ml/kg/min [2, 3].

Postoperative Follow-Up

The postoperative period (30 days) was recorded for complications (as defined in table 1) [1]. For patients with a pre-operatively elevated PaCO₂ (>45 mm Hg) a further retention of ≥5 mm Hg was considered a complication. The duration of hospital stay was calculated from 1 day prior to surgery until discharge. The intermediate-term outcome was assessed at 6 months with a clinical examination, a chest roentgenogram, measurement of PFT and symptom-limited cycle ergospirometry.

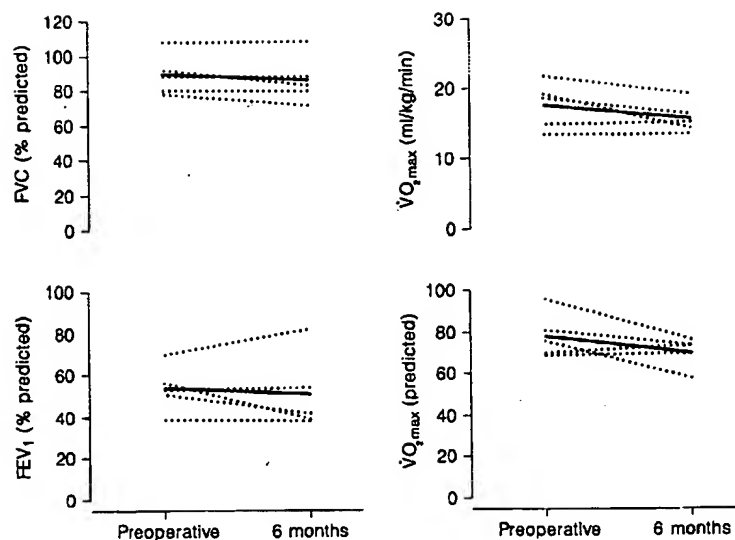
Results

The results of all pre-operative functional tests of the 5 high-risk patients are listed in table 2. The additional measurement of PH would have excluded 4 patients (No. 2-5) from surgery if the cut-off value for PAP of ≥35 mm Hg and PVR of ≥190 dyn·s·cm⁻⁵ on exercise had been applied. All 5 patients were able to complete the cycle ergospirometry to exhaustion. No cardiac arrhythmias or changes in the ST-T segments were observed during exercise or in the recovery phase.

VO_{2max} taken in absolute values would have excluded 2 female patients (No. 2 and 3) from surgery if the cut-off value of <15 ml/kg/min had been applied. Analysed on a percent of predicted basis, VO_{2max} of all 5 patients was ≥69% (table 2), indicating only mild impairment of exercise capacity in the 2 women with a VO_{2max} of <15 ml/kg/min. We therefore overruled the absolute values of ≥15 ml/kg/min for these 2 patients based on our previous experience since the inception of pre-operative exercise testing at our institution.

Thus, all 5 high-risk patients were deemed operable and underwent lobectomy. All procedures were curative as the tumours were histologically confirmed stage I and II disease; the one patient with small-cell lung cancer

Fig. 1. Pre- and postoperative cardio-pulmonary function in 5 patients undergoing lobectomies for bronchogenic carcinoma. = Individual patients; — = mean value. There was no significant difference between pre-operative and 6-month postoperative values of FVC, FEV₁ and VO_{2max}.



underwent adjuvant chemotherapy although no metastases could be detected at the time of surgery. The lobe resected, the histology and the total hospital stay for each patient are indicated in table 2. The postoperative course was uneventful apart from one prolonged air leak (10 days). The mean hospital stay was 16 days (range: 13–21). All 5 patients underwent a complete re-evaluation at 6 months postoperatively. Figure 1 shows that there was no difference between pre- and postoperative functional status as assessed by FVC, FEV₁ and VO_{2max} ($p > 0.05$, Wilcoxon test for paired differences). Three of the 5 patients estimated their physical condition to be better than before the operation which they attributed to their having quit smoking and started regular exercising, 2 patients felt worse at 6 months due to a current exacerbation of their chronic obstructive pulmonary disease. No signs of tumour recurrence were found at 6 months.

Discussion

Marginal cardiopulmonary reserves in lung resection candidates are often a limiting factor for operability. In bronchogenic carcinoma the gold standard for curative surgery remains resection of not less than a lobe. Segmental or wedge resections have been proposed for pa-

tients with stage I disease and borderline PFT [18, 19], but the local recurrence rate is higher for sublobar resections [20]. The progress in surgical and anaesthetic techniques allows us to consider operative procedures in patients who would have been considered functionally inoperable a few years ago. Further, the pre-operative assessment of high-risk patients has evolved dramatically over the last decade. Apart from various PFT it has been routine practice in many institutions to measure PH in high-risk patients. It was reported that an increased PAP at rest or pressures ≥ 35 mm Hg at moderate exercise [14, 16, 17], as well as an elevated PVR of ≥ 190 dyn·s·cm⁻⁵ at rest or at moderate exercise [15] indicated a high risk for surgery. In these patients a reduction of the pulmonary vascular bed would not only cause peri-operative complications but also disabling dyspnoea due to a permanent postoperative increase in their pulmonary arterial hypertension [16]. However, the value of the measurement of PH remains controversial [7]; in a large group of 234 patients, Loddenkemper et al. [21] showed that those with pressures exceeding 35 mm Hg did not have more postoperative complications than those with lower pressures. Similar results were reported by Konietzko et al. [22].

Recently an increasing number of reports about the value of exercise testing and more specifically the measurement of VO_{2max} has been published. Most of them find

$\dot{V}O_{2\max}$ a useful parameter [1-3, 23], others see no discriminating value for complications [4, 5]. Since the paper of Smith et al. [2] in 1984 there seems to be some agreement, however, that a $\dot{V}O_{2\max}$ of <15 ml/kg/min represents a high risk and one of >20 ml/kg/min a very low risk for postoperative complications. B  chard and Wetstein [1] concluded that <10 ml/kg/min excluded any pulmonary resection. The range between 10 and 20 ml/kg/min remains a grey zone, and most recently Morice et al. [3] chose a cut-off value of 15 ml/kg/min assuming thereby that values between 10 and 15 ml/kg/min represented an unacceptably high risk. Myoshi et al. [24] found that the oxygen consumption/body surface area at an arterial lactate level of 20 mg/dl ($\dot{V}O_2/BSA$ at La-20) did not differ between patients with and without pulmonary complications but was an important indicator of postoperative mortality. Interestingly enough only the two studies by Smith et al. [2] and Markos et al. [5] reported $\dot{V}O_{2\max}$ both in absolute values as well as expressed as a percent of predicted, the absolute values being more useful.

When we tested our 5 high-risk patients we therefore performed the traditional measurement of PH on the one hand and analysed our cycle ergospirometry $\dot{V}O_{2\max}$ both in absolute values as well as a percent of predicted. When we chose the criteria of eligibility for lobectomy we relied on published data as far as PH [14-17] and absolute values for $\dot{V}O_{2\max}$ [2] were concerned. The rationale behind also including percent of predicted $\dot{V}O_{2\max}$ values was that most prediction equations account for age and sex, which are the most important determinants of exercise capacity [11-13]. Expressed in absolute values only, $\dot{V}O_{2\max}$ would have excluded 2 patients in our study. Both were elderly women whose predicted values are lower than those of men of the same age group. Our previous experience with lobectomies had been good in patients with a $\dot{V}O_{2\max}$ of <15 ml/kg/min provided that, expressed as a percent of predicted, $\dot{V}O_{2\max}$ was fairly well preserved (mean value 64%). As all 5 patients had reached a $\dot{V}O_{2\max}$ value of $\geq 69\%$ of predicted, their exercise capacity was at the most mildly impaired. This was in striking contrast to the marginal PFT and PH measurements. We therefore arbitrarily decided to consider all 5 patients operable for lobectomies.

The postoperative course of all 5 patients was uneventful, and all had been discharged 3 weeks after the operation. Figure 1 illustrates that the intermediate-term follow-up showed no functional deterioration although there was a downward trend in $\dot{V}O_{2\max}$. In our opinion $\dot{V}O_{2\max}$ might well represent the single best global parameter of

cardiopulmonary reserve and may therefore allow us to overrule all other established criteria of functional operability. The excellent postoperative outcome in these patients with severely impaired pulmonary function and pulmonary arterial hypertension confirmed the value of non-invasive exercise testing in the decision-making process.

A clear shortcoming of our study is the small sample size which does not allow to draw any statistical conclusions about the superior value of exercise testing over the measurement of PH. Therefore, prospective studies with larger sample sizes are needed to compare the two methods. Our observations indicate, however, that in the mean time lung resection candidates with poor PFT should not be excluded from operation on the basis of PH but rather be given the chance to 'qualify' through an additional maximal exercise test. For the same reason of a small sample size our results do not allow us to propose any new $\dot{V}O_{2\max}$ cut-off value for operability. Nevertheless, our findings seem to indicate that a $\dot{V}O_{2\max}$ in the range of 2/3 of predicted might represent the lower limit.

Our patients were exercised on a bicycle ergospirometer, which is fairly expensive equipment. Holden et al. [6] showed that a 6-min walking distance of $>1,000$ feet (333 m) and a stair climb of >44 steps (11 steps/flight) were predictive of a successful outcome in a group of lung resection candidates with an FEV_1 of ≤ 1.6 litres. Pollock et al. [25] recently demonstrated in patients with chronic airflow obstruction that 4.6 flights of stair climbing corresponded to a $\dot{V}O_2$ of 20 ml/kg/min which would guarantee safe thoracotomy [1, 2]. This might allow to substitute ergospirometry for a much simpler and cheaper walking or stair climbing test. In our opinion, one caveat must be remembered, however. Some of the patients with severely limited PFT also have coronary artery disease which makes continuous measurement of the ECG and the presence of a defibrillator mandatory during a maximal stress test. These requirements are more difficult to fulfil with walking tests than with stationary ergospirometry equipment. We therefore feel that if ergospirometry is available it represents the safer test modality to assess exercise capacity.

In conclusion, in our subgroup of patients deemed inoperable according to established PFT criteria the addition of PH was not helpful in assessing operability. Only exercise testing with the determination of $\dot{V}O_{2\max}$ expressed as a percent of predicted indicated functional operability, which permitted curative lobectomy in all patients. These preliminary results indicate that future prospective studies for the assessment of functional operability in lung

resection candidates should include $\text{VO}_{2\text{max}}$ both in absolute and in percent of predicted values. This global test of cardiopulmonary reserve might give more lung cancer patients with marginal PFT the chance of curative resection.

Acknowledgements

This study was supported by grants from the Swiss Society of Pneumology and the Foundation for Pneumology, Basel, Switzerland.

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• Ann Thorac Surg 1998 Dec;66(6):2164



FULL-TEXT ARTICLE

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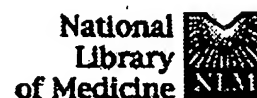
Predictive respiratory complication quotient predicts pulmonary complications in thoracic surgical patients.

Melendez JA, Barrera R.

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Related Resources

BACKGROUND: This study was designed to develop an accurate preoperative index of prediction of outcome and hospital charges after lung resection with standard available pulmonary tests in a tertiary cancer center. **METHODS:** Sixty-one consecutive patients undergoing pulmonary resections were evaluated. All patients underwent spirometry, carbon monoxide diffusion capacity, split lung function testing, and room air blood gas analysis at rest and after a 2-minute step climb. The thoracic prospective data base and patient charts were reviewed for length of hospitalization, postoperative length of stay, and complications requiring therapy. Logistic regression analysis of the preoperative data, operation and postoperative outcome was used to develop a new postoperative predictive index: the predictive respiratory complication quotient (PRQ). We describe the design of the equation for the probability of serious pulmonary complications, hospital stay, and hospital charges based on PRQ. **RESULTS:** Ten of 12 patients with a PRQ less than 2,200 suffered serious pulmonary complications of pneumonia, respiratory insufficiency, hypoxemia, and death. Forty-nine patients with a PRQ more than 2,200 did not experience any pulmonary complications. Postoperative length of stay and hospital charges correlated with the PRQ. **CONCLUSIONS:** A construct such as the PRQ may provide a better prediction of outcome than its individual parts. We identified an important underlying relationship between intensive care unit stay, hospital stay and charges, and our index. A PRQ of less than 2,200 was associated with an increased risk of pulmonary complications and mortality.



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☐ 1: J Thorac Cardiovasc Surg 1997 Dec;114(6):957-64;
discussion 964-7Related Articles
Links**J Thorac Cardiovasc Surg****Patient selection criteria for lung volume reduction surgery.**

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McKenna RJ Jr, Brenner M, Fischel RJ, Singh N, Yoong B, Gelb AF, Osann KE.

Lung Center, Chapman Medical Center, Orange, Calif., USA.

Related Resources

OBJECTIVE: Our intent was to refine the patient selection criteria for lung volume reduction surgery because various centers have different criteria and not all patients benefit from the procedure. **METHODS:** Patient information, x-ray results, arterial blood gases, and plethysmographic pulmonary function tests in 154 consecutive patients who underwent bilateral thoracoscopic stapled lung volume reduction surgery were compared with clinical outcome (change in forced expiratory volume in 1 second and dyspnea scale) with t tests and analysis of variance. **RESULTS:** Three hundred thirty-three of 487 (69%) patients evaluated for lung volume reduction surgery were rejected for lack of heterogeneous emphysema (n = 212), medical contraindications (n = 88), hypercapnia (n = 20), uncontrolled anxiety or depression (n = 10), or pulmonary hypertension (n = 1). Two patients died during the evaluation process. When tested by analysis of variance, there was no difference in clinical outcome associated with preoperative forced expiratory volume in 1 second, residual volume, total lung capacity, single-breath diffusing, and arterial oxygen or carbon dioxide tension. All patients selected for the operation had a heterogeneous pattern of emphysema. The upper lobe heterogeneous pattern of emphysema on chest computed tomography and lung perfusion scan was strongly associated with improved outcome with a mean (95% confidence interval) improvement in forced expiratory volume in second of 73.2% (63.3 to 83.1) for the upper lobe compared with a mean (95% confidence interval) improvement of 37.9% (22.9 to 53.0) for the lower lobe or diffuse pattern of emphysema. **CONCLUSION:** The most important selection criteria for lung volume reduction surgery is the presence of a bilateral upper lobe heterogeneous pattern of emphysema on chest computed tomography and lung perfusion scan. After patients have been selected on the basis of a heterogeneous pattern of emphysema, clinical factors and physiology are not associated with clinical outcome well enough to further

TOWNSEND *and* TOWNSEND *and* CREW LLP



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,068	12/13/2001	Rodney A. Perkins	017534-000730US	7372

20350 7590 02/19/2003

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EXAMINER

THOMPSON, KATHRYN L

ART UNIT

PAPER NUMBER

3763

DATE MAILED: 02/19/2003

Response Due 5/19/03 53P

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/017,068	Applicant(s) PERKINS ET AL.	
	Examiner Kathryn L Thompson	Art Unit 3763	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>2</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(e) as being anticipated by Medhkour et al (US 6,493,589). Medhkour et al discloses a method of reducing lung size of a lung, including the steps of inserting a conduit down a trachea, into a mainstem bronchus, into a bronchial branch, and into a bronchial sub-branch communicating with a lung portion of the lung to be reduced in size, pulling a vacuum in the lung portion through the conduit to collapse the lung portion and deploying an obstructing member in the bronchial sub-branch to preclude air from being inhaled into the lung portion through the bronchial sub-branch (Column 9, Lines 5-8; Column 11, Lines 40-52; Column 12, Lines 13-23; Column 12, Lines 63-67).

Art Unit: 3763

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medhkour et al in view of Dayal (US 5,660,175). Medhkour et al teaches all of the claimed limitations except the step of advancing the obstructing member/plug through a conduit/catheter and into the bronchial sub-branch/air passage. Dayal discloses advancing the obstructing member/plug (7) through a conduit/catheter (1) and into the bronchial sub-branch/air passage (Column 8, Lines 27-50; Figure 12E). It would have been obvious to one with ordinary skill in the art to use the teachings of Dayal to modify the invention of Medhkour et al and advance the obstructing member of Medhkour et al down a catheter/conduit of Dayal since the inflatable cuff on the catheter/conduit of Dayal can provide the effect of stabilizing and sealing the catheter/conduit to the trachea before the inflating of Medhkour et al's obstructing member.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathryn L Thompson whose telephone number is 703-305-3286. The examiner can normally be reached on 8:30 AM - 6:00 PM: 1st Friday Off.

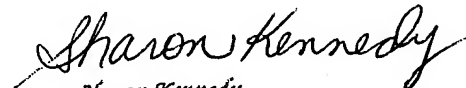
Art Unit: 3763

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on 703-308-3552. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9302 for regular communications and 703-872-9303 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0858.

KLT

February 9, 2003


Sharon Kennedy
Primary Examiner

Notice of References Cited

Application/Control No.

10/017,068

Applicant(s)/Patent Under
Reexamination
PERKINS ET AL.

Examiner

Kathryn L Thompson

Art Unit

3763

Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,493,589	12-2002	Medhkour et al.	604/114
	B	US-5,660,175	08-1997	Dayal, Bimal	128/207.15
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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FOREIGN PATENT DOCUMENTS

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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet

1

of

Complete if Known

Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

U.S. PATENT DOCUMENTS

Examiner Initials *	Cite No. ¹	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code ² (if known)			
KZ	A	3,322,126		Rüsch et al.	05/30/1967	
	B	3,498,286		Polanyi et al.	03/03/1970	
	C	3,669,098		Takahashi	06/13/1972	
	D	3,677,262		Zukowski	07/18/1972	
	E	3,776,222		Smiddy	12/04/1973	
	F	3,866,599		Johnson	02/18/1975	
	G	3,913,568		Carpenter	10/21/1975	
	H	4,041,936		Carden	08/16/1977	
	I	4,086,919		Bullard	05/02/1978	
	J	4,327,720		Bronson et al.	05/04/1982	
	K	4,327,721		Goldin et al.	05/04/1982	
	L	4,453,545		Inoue	06/12/1984	
	M	4,468,216		Muto	08/28/1984	
	N	4,567,882		Heller	02/04/1986	
	O	4,716,896		Ackerman	01/05/1988	
	P	4,742,819		George	05/10/1988	
	Q	4,784,133		Mackin	11/15/1988	
	R	4,819,664		Nazari	04/11/1989	
	S	4,846,153		Berci	07/11/1989	
	T	4,850,371		Broadhurst et al.	07/25/1989	
	U	4,862,874		Kellner	10/05/1989	
	V	4,896,941		Hayashi et al.	01/30/1990	
	W	4,949,716		Chenoweth	08/21/1990	
	X	4,955,375		Martinez	10/11/1990	
	Y	4,958,932		Kegelman et al.	10/25/1990	
	Z	4,961,738		Mackin	10/09/1990	
	AA	4,976,710		Mackin	12/11/1990	
	AB	5,056,529		de Groot	10/15/1991	
	AC	5,143,062		Peckham	10/01/1992	
	AD	5,146,916		Catalani	09/15/1992	
	AE	5,165,420		Strickland	11/1992	

Examiner
Signature*Kathryn L. Thompson*Date
Considered

02/09/03

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¹ Unique citation designation number. ² See attached Kinds of U.S. Patent Documents. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

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Sheet

2

of

Complete if Known

Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

U.S. PATENT DOCUMENTS

Examiner Initials *	Cite No. ¹	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code ² (if known)			
KSP	AF	5,285,778		Mackin	02/15/1994	
	AG	5,309,903		Long	05/10/1994	
	AH	5,331,947		Shturman	07/26/1994	
	AI	5,361,753		Pothmann et al.	11/08/1994	
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	AN	5,642,730		Baran	07/01/1997	
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	AP	5,653,231		Bell	08/05/1997	
	AQ	5,660,175		Dayal	08/26/1997	
	AR	5,682,880		Brain	11/04/1997	
	AS	5,707,352		Sekins et al.	01/13/1998	
	AT	5,752,921		Orr	05/19/1998	
	AU	5,893,841		Glickman	04/13/1999	
	AV	5,897,528		Schultz	04/27/1999	
	AW	6,174,323		Biggs et al.	6,174,323	
	AX	6,258,100		Alfermess et al.	6,258,100	

FOREIGN PATENT DOCUMENTS

Examiner Initials *	Cite No. ¹	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Office ³	Number ⁴	Kind Code ⁵ (if known)				
KSP	AY	WIPO	WO 92/10971			09/07/1992		
	AZ	WIPO	WO 95/33506			14/12/1995		
	BA	WIPO	WO 98/48706			05/11/1998		
	BB	WIPO	WO 98/49191			05/11/1998		
	BC	WIPO	WO 99/01076			14/01/1999		
	BD	WIPO	WO 99/17827			15/04/99		

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Kathryn L. Thompson

Date
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Sheet 3 of

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Application Number	
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
Kathryn A. Thompson	BE	Becker et al., "Lung volumes before and after lung volume reduction surgery" Am. J. Respir. Crit. Care Med. (1998) 157:1593-1599.	
	BF	Clark et al., "Lung volume reduction surgery alters management of pulmonary nodules in patients with severe COPD" Chest (1997) 112(6):1494-1500.	
	BG	Coryllos and Bimbaum, "Studies in pulmonary gas absorption in bronchial obstruction. I. Two new methods for direct and indirect observation." Amer. J. Med. Sci. (1932) 183:317-326.	
	BH	Coryllos and Bimbaum, "Studies in pulmonary gas absorption in bronchial obstruction. II. The behavior and absorption times of oxygen, carbon dioxide, nitrogen, hydrogen, helium, ethylene, nitrous oxide, ethyl chloride, and ether in the lung." Amer. J. Med. Sci. (1932) 183:326-347.	
	BI	Coryllos and Bimbaum, "Studies in pulmonary gas absorption in bronchial obstruction. III. A theory of air absorption in atelectasis." Amer. J. Med. Sci. (1932) 183:347-359.	
	BJ	Criner et al., "Effect of lung volume reduction surgery on diaphragm strength" Am. J. Res. Crit. Care Med. (1998) 157:1578-1585.	
	BK	Harada et al., "Re-expansion of refractory atelectasis using a bronchofiberscope with a balloon cuff" Chest (1983) 84(6):723-728.	
	BL	Kotloff et al., "Comparison of short-term functional outcomes following unilateral and bilateral lung volume reduction surgery" Chest (1998) 113(4):890-895.	
	BM	Sclafani, "Clearing the airways" AARC Times (January 1999) pp. 69-71, 97.	

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Examiner Signature	Kathryn A. Thompson	Date Considered	02/09/03
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017534-000730US JMH

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/017,068	12/13/2001	3763	370	017534-000730US	16	5	2

CONFIRMATION NO. 7372

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Date Mailed: 03/29/2002

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Applicant(s)

Rodney A. Perkins, Woodside, CA; ✓
Peter P. Soltesz, San Jose, CA; ✓
Robert Kotmel, Burlingame, CA; ✓

Assignment For Published Patent Application

PULMONX, Palo Alto, CA;

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CON OF 09/606,320 06/28/2000 ✓
WHICH IS A CIP OF 09/347,032 07/02/1999 PAT 6,287,290 ✓

Foreign Applications

If Required, Foreign Filing License Granted 01/02/2002

Projected Publication Date: 04/11/2002

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

Methods, systems, and kits for lung volume reduction

Preliminary Class

604

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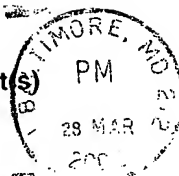
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Application No. 10/017,068

File No. 17534-000730US

Date Due 03/18/02

Date Mailed JMH:bjl

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PATENT
Attorney Docket No.: 017534-000730US

By: 
Brad J. Loos

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Rodney A. Perkins et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION

Examiner: Unassigned

Art Unit: 3763

REQUEST FOR CORRECTED FILING
RECEIPT

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Office of Initial Patent Examination
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Washington, D.C. 20231

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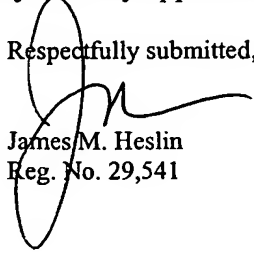
There is an error in that the Domestic Priority data as claimed by applicant should read as follows:

THIS APPLICATION IS A CON OF 09/606,320 06/28/2000

WHICH IS A CIP OF 09/347,032 07/02/1999 PAT 6,287,290

The correction is not due to any error by applicant and no fee is due.

Respectfully submitted,


James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
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San Francisco, California 94111-3834
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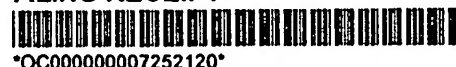
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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/017,068	12/13/2001	3763	370	017534-000730US	16	5	2

CONFIRMATION NO. 7372

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Applicant(s)

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 Peter P. Soltesz, San Jose, CA;
 Robert Kotmel, Burlingame, CA;

Assignment For Published Patent Application

PULMONX, Palo Alto, CA;

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CON OF 09/606,320 06/28/2000
 WHICH IS A CIP OF 09/347,032 07/02/1999 PAT 6,287,290
~~WHICH IS A DIV OF 09/379,972 08/24/1999 PAT 6,293,951~~

Foreign Applications

If Required, Foreign Filing License Granted 01/02/2002

Projected Publication Date: 04/11/2002

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

Methods, systems, and kits for lung volume reduction

Preliminary Class

604

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Title 37, Code of Federal Regulations, 5.11 & 5.15**

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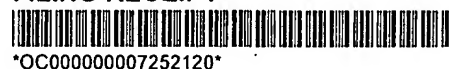
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By: 
Brad J. Loos

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: 10/017,068

Filed: December 13, 2001

For: METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION

Examiner: Unassigned

Art Unit: Unassigned

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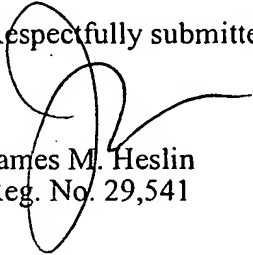
The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. In accordance with 37 CFR §1.98(d), copies of the references can be found in Application No. 09/606,320, filed June 28, 2000 (Attorney Docket No. 17534-000710US). It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

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Respectfully submitted,


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Sheet 1

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Application Number	10/017,068
Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	017534-000730US

U.S. PATENT DOCUMENTS

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	A	3,322,126		Rüsch et al.	05/30/1967	
	B	3,498,286		Polanyi et al.	03/03/1970	
	C	3,669,098		Takahashi	06/13/1972	
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	AD	5,146,916		Catalani	09/15/1992	
	AE	5,165,420		Strickland	11/1992	

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			Filing Date	December 13, 2001
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	AG	5,309,903		Long	05/10/1994	
	AH	5,331,947		Shturman	07/26/1994	
	AI	5,361,753		Pothmann et al.	11/08/1994	
	AJ	5,400,771		Pirak et al.	03/28/1995	
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	AY	WIPO	WO 92/10971			09/07/1992		
	AZ	WIPO	WO 95/33506			14/12/1995		
	BA	WIPO	WO 98/48706			05/11/1998		
	BB	WIPO	WO 98/49191			05/11/1998		
	BC	WIPO	WO 99/01076			14/01/1999		
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	BE	Becker et al., "Lung volumes before and after lung volume reduction surgery" Am. J. Respir. Crit. Care Med. (1998) 157:1593-1599.	
	BF	Clark et al., "Lung volume reduction surgery alters management of pulmonary nodules in patients with severe COPD" Chest (1997) 112(6):1494-1500.	
	BG	Coryllos and Birnbaum, "Studies in pulmonary gas absorption in bronchial obstruction. I. Two new methods for direct and indirect observation." Amer. J. Med. Sci. (1932) 183:317-326.	
	BH	Coryllos and Birnbaum, "Studies in pulmonary gas absorption in bronchial obstruction. II. The behavior and absorption times of oxygen, carbon dioxide, nitrogen, hydrogen, helium, ethylene, nitrous oxide, ethyl chloride, and ether in the lung." Amer. J. Med. Sci. (1932) 183:326-347.	
	BI	Coryllos and Birnbaum, "Studies in pulmonary gas absorption in bronchial obstruction. III. A theory of air absorption in atelectasis." Amer. J. Med. Sci. (1932) 183:347-359.	
	BJ	Criner et al., "Effect of lung volume reduction surgery on diaphragm strength" Am. J. Res. Crit. Care Med. (1998) 157:1578-1585.	
	BK	Harada et al., "Re-expansion of refractory atelectasis using a bronchofiberscope with a balloon cuff" Chest (1983) 84(6):725-728.	
	BL	Kotloff et al., "Comparison of short-term functional outcomes following unilateral and bilateral lung volume reduction surgery" Chest (1998) 113(4):890-895.	
	BM	Sclafani, "Clearing the airways" AARC Times (January 1999) pp. 69-71, 97.	

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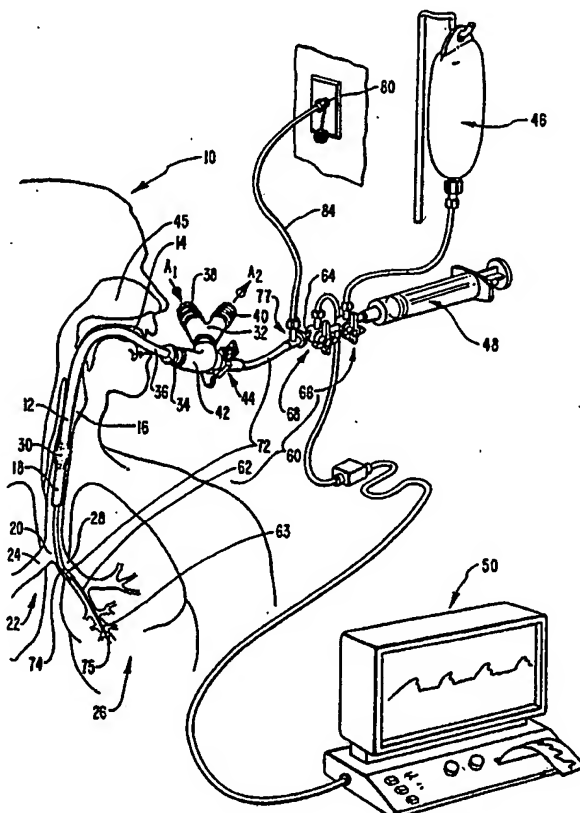
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61B 5/00	A1	(11) International Publication Number: WO 92/10971 (43) International Publication Date: 9 July 1992 (09.07.92)
<p>(21) International Application Number: PCT/US91/09732</p> <p>(22) International Filing Date: 20 December 1991 (20.12.91)</p> <p>(30) Priority data: 631,638 21 December 1990 (21.12.90) US 810,379 19 December 1991 (19.12.91) US</p> <p>(71) Applicant: BALLARD MEDICAL PRODUCTS [US/US]; 12050 Lone Peak Parkway, Draper, UT 84020 (US).</p> <p>(72) Inventor: STRICKLAND, Richard, D. ; 8890 South Sheffield Way, Sandy, UT 84093 (US).</p> <p>(74) Agent: NYDEGGER, Rick, D.; 1000 Eagle Gate Tower, 60 East South Temple, Salt Lake City, UT 84111 (US).</p>		<p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: BRONCHOALVEOLAR LAVAGE CATHETER

(57) Abstract

An outer catheter (72) so sized and configured so as to extend from a point below the first bifurcation of the trachea through the upper respiratory system of the patient is disposed about an inner catheter (62) having a tip (75) secured in the opening at the distal end (74) thereof with an outer lateral periphery larger in diameter than the outer surface of the inner catheter. A passageway (76) is formed between said outer catheter (72) and said inner catheter (62). A connector hub assembly (77), connected to the proximal end (73) of the outer catheter (72) and couplable to a supply of oxygen, allows for oxygen insufflation to take place during the bronchoalveolar lavage procedure. The proximal surface of the tip (75) between the outer lateral periphery and the outer surface of the inner catheter (62) is capable of sealingly engaging the distal end (74) of the outer catheter (72). In this condition the pair of catheters can be advanced through the upper respiratory system of the patient without contaminating the outer surface of the inner catheter (62). Thereafter the inner catheter (62) is advanced relative to the outer catheter (72) into a wedging position in a bronchiole of the patient. In one embodiment, the inner catheter is provided with a selectively inflatable cuff by which to engage the walls of a bronchiole of the patient.



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BRONCHOALVEOLAR LAVAGE CATHETER

1. Field of the Invention

This invention relates to the diagnosis of abnormal conditions in the lungs, and to a catheter by which to conduct bronchoalveolar lavage. More particularly the present invention relates to a method and apparatus for conducting bronchoalveolar lavage without the use of a bronchoscope.

2. Background Art

The technique of bronchoalveolar lavage has become common in the diagnosis of infections and other abnormalities in the alveoli at the terminus of the bronchiole in the lungs of a patient. In bronchoalveolar lavage, occasionally referred to as "BAL", a sterile fluid is infused in aliquots of about 30 ml. each through the upper respiratory system of a patient into the portion of the lungs thereof designated for study. The fluid infused is then aspirated and cultured and examined in order to isolate and identify infections, fungi, cells, and other signs of inflammation thusly flushed from the walls of the alveoli. Only about 40-60% of each infused aliquot can be aspirated. Thus in studies which require large volumes of aspirated fluid, a total infusion of from 30 to about 500 ml. may be required. A helpful background statement on the nature and useful findings related to the use of bronchoalveolar lavage is the American Thoracic Society, "Clinical Role of Bronchoalveolar Lavage in Adults with Pulmonary Disease", 142 AMERICAN REVIEW OF RESPIRATORY DISEASE, 481-486 (1990).

In order to effect the infusion of solution, it has in the past been the practice to utilize a bronchoscope to visually observe the advancement of a catheter through the upper respiratory system of a patient and the branching of

the bronchi into a selected bronchiole. During this advancement process, the size of the air passage through which the distal tip of the bronchoscope is advanced gradually decreases until the distal tip of the bronchoscope wedges within the walls of a single bronchiole. This wedge is visually inspected using the bronchoscope, and thereafter the infusion and aspiration of solution is effected through the working lumen of the bronchoscope.

Drawbacks arise, however, in relation to the use of a bronchoscope in this procedure. First, the bronchoscope itself is a very expensive piece of equipment. As a result, it is not practical to dispose of the device following a single use. Instead the bronchoscope must be reused in order to distribute its expense over a number of procedures. Routine heat based sterilization cannot be used, however. Instead procedures must be employed which are particularly adapted to the delicate nature of the materials comprising the bronchoscope. These sterilization procedures are approximately 24 hours in duration, so that a single costly bronchoscope can be utilized at a given medical establishment only once a day. Thus, a plurality of bronchoscopes must be maintained by a medical establishment if the establishment is to have the opportunity to perform bronchoalveolar lavage more than once a day.

In addition to being extremely delicate in the face of normal sterilization conditions, bronchoscopes are very susceptible to breakage through incorrect use. Like the device itself, repairs on the bronchoscope are extremely expensive. A reference discussing the sources of damage to flexible fiber optic bronchoscopes is Mehta, et al., "The High Price of Bronchoscopy: Maintenance and Repair of the Flexible Fiber Optic Bronchoscope", 98 CHEST 448-54 (August 1984), which is incorporated herein by reference.

1 Recent literature has forecast a rise in the frequency
with which medical practitioners can be expected to resort
to the use of bronchoalveolar lavage. The increased
incidence of acquired immune deficiency syndrome (AIDS) and
5 other therapeutic-related immunocompromising treatments,
such as chemotherapy, gives rise to a large number of
patients susceptible to multiple and exotic lung
infections. An accurate diagnosis of the identity of these
infections is essential, if the patient is to be
10 effectively medicated. Typical of the literature
discussing efforts at isolating lung infections in AIDS and
other immunocompromised patients are the following:

15 Caughley, et al., "Non-Bronchoscopic
Bronchio Alveoli Lavage for the Diagnosis of
Pneumocystitis Carinii Pneumonia in the Acquired
Immune Deficiency Syndrome", 88 CHEST 659-62
(November 1985).

20 Sobonya, et al., "Detection of Fungi and
other Pathogens in Immunocompromised Patients by
Bronchio Alveoli Lavage in an Area Endemic for
Coccidioidomycosis", 97 CHEST 1349-55
(June 1990).

 Guerra, et al., "Use of Bronchio Alveoli
Lavage to Diagnose Bacterial Pneumonia in
Mechanically Ventilated Patients", 18 CRITICAL
CARE MEDICINE 169-73 (1990).

25 Some difficulties have also been experienced in
effecting a clear diagnosis of conditions in the lung due
to contamination of the equipment for conducting the
bronchoalveolar lavage as the distal end of that equipment
is passed through the upper respiratory system of a patient
30 to the lung segment selected for study. In the process of
that passage, the exterior of the distal end of the
catheter by which infusion and aspiration is actually
effected becomes contaminated with micro-organisms in the
upper respiratory system of the patient. As a result, the
35 fluid samples aspirated from the lungs thereafter are

frequently compromised by cultures of organisms not actually located in the alveoli.

When a bronchoscope is not utilized, problems have been experienced in locating the distal tip of the sampling catheter in a specific preselected lung to be studied, placement in the left lung being particularly difficult due to inherent anatomical structure of the bronchi. Fluoroscopic and X-ray methods for verifying the location of a distal tip can to an extent be useful in assisting and directing the distal tip into a specific preselected lung, but these methods are totally incapable of replacing the primary value of bronchoscope use, namely the verification of distal tip wedging in a bronchi of the patient to the extent required for successful infusion and aspiration of fluid. Fluoroscopic and X-ray methods for effecting placement are also complicated to utilize, and may be limited by availability to large medical institutions.

A further problem which may occur during bronchoscopy is oxygen desaturation within the lungs. People who are restricted in their respiratory capacity, such as people with lung disease or those in an active pneumonia situation, may have a difficult time in maintaining their oxygen saturation throughout the bronchoalveolar lavage procedure. As such, supplemental oxygen must be provided. Currently, the patient may receive supplemental oxygen either by a nasal cannula or by an oxygen catheter which is slid through one of the nostrils and placed at the back of the throat above the vocal chords. With each added need for oxygen, the rate of flow of the supplemented oxygen may be increased from two liters to four liters, four liters to six, six liters to eight, and so on. Unfortunately, from increasing oxygen flow arises increased turbulence and irritation, along with the possibility that there may still be a transient drop in oxygen saturation even with the increased flow. This may occur as oxygen may be wasted

1 along the passageway through the nose and the mouth and so
on, before reaching the lungs. Therefore, in the prior
art, oxygen insufflation cannot be executed with efficiency
and success during the bronchoalveolar lavage procedure.

BRIEF SUMMARY AND OBJECTS OF THE INVENTION

One object of the present invention is to improve the
accuracy of diagnostic efforts directed to inflammations
and other abnormalities in the lungs.

10 It is a related object of the present invention to
increase the ease and reduce the costs of conducting
bronchoalveolar lavage.

Another object of the present invention is to
facilitate the use of bronchoalveolar lavage without resort
15 to costly bronchoscopic techniques.

It is another object of the present invention to
permit frequent bronchoalveolar lavage sampling.

Yet another object of the present invention is to
produce a bronchoalveolar lavage catheter which is
20 adequately inexpensive to produce so as to be disposable.

Another object of the present invention is a
disposable bronchoalveolar lavage catheter which does not
require the use of a bronchoscope to confirm proper
placement of the catheter prior to infusion and aspiration.

25 Yet another object of the present invention is to
provide a bronchoalveolar catheter which is capable of
being located in one or the other of the lungs with a high
degree of reliability.

Yet another object of the present invention is to
30 prevent contamination of the exterior surface of a catheter
by which bronchoalveolar lavage is being conducted during
the passage of that catheter through the upper respiratory
system of the patient.

It is yet another object of the present invention to
35 produce a bronchoalveolar lavage catheter as described

which is useable in patients with or without mechanical ventilation.

It is an object of the present invention to permit bronchoalveolar lavage sampling of lung segments of varying sizes.

It is a further object of the present invention to provide a bronchoalveolar lavage catheter which allows oxygen insufflation during the bronchoalveolar lavage procedure.

Additional objects and advantages of the invention will be set forth in the description which follows, and in part will be obvious from the description, or may be learned by the practice of the invention. The objects and advantages of the invention may be realized and obtained by means of the instruments and combinations particularly pointed out in the appended claims.

To achieve the foregoing objects, and in accordance with the invention as embodied and broadly described herein an apparatus and method are provided for conducting bronchoalveolar lavage without the use of bronchoscopy. Accordingly, a catheter is provided comprising an outer catheter and an inner catheter disposable therein, wherein a passageway between said outer catheter and said inner catheter is formed. The outer catheter is so sized and configured as to extend from a point below the first bifurcation of the trachea of a patient through the upper respiratory system of the patient. The distal end of the outer catheter departs from the longitudinal axis thereof at a predetermined bend angle. The proximal end of the outer catheter may be connected to a connector hub assembly comprised of an oxygen insufflation hub and a sealing hub. The oxygen insufflation hub is couplable to a supply of oxygen such that oxygen may be passed through the insufflation hub to the passageway between the outer catheter and the inner catheter and on to the trachea. The

1 sealing hub is comprised of a silicone washer which
encircles the inner catheter and seals the connector hub
assembly such that oxygen is allowed to pass in only one
direction within the outer catheter.

5 The inner catheter is so sized and configured as to
extend from a bronchiole in the lung of the patient through
the upper respiratory system of the patient. The distal
end of the inner catheter wedges at whatever level of
10 bronchi branching in the lung is appropriate according to
the size of the inner catheter. The catheter further
comprises means located at the proximal end of the inner
catheter for infusing and aspirating fluid through the
inner catheter.

15 Typically the means for infusing and aspirating
comprises a sampling stopcock located at the proximal end
of the sampling catheter. The sampling stopcock is
connectable to a reservoir of a fluid and to a syringe for
infusing the fluid through the inner catheter. The
20 sampling stopcock is capable of placing the syringe
alternately in communication with the reservoir of fluid or
with the proximal end of the inner catheter.

According to another aspect of the invention, the
inner catheter comprises a first closure means located at
the distal end of the inner catheter for sealing the distal
25 end of the outer catheter when the outer catheter is
disposed encircling the inner catheter with the distal end
of the inner catheter at the distal end of the outer
catheter. In the embodiment disclosed herein, the first
closure means comprises a tip at the distal end of the
30 inner catheter. The tip has an outer lateral periphery
having a diameter greater than the outer surface of the
inner catheter. Between the outer lateral periphery of the
tip and the outer surface of the inner catheter the tip has
a proximal surface which is capable of sealingly engaging
35 the distal end of the outer catheter when the outer

catheter is disposed encircling the inner catheter with the distal end of the inner catheter at the distal end of the outer catheter. An aperture is centrally formed through the tip of the inner catheter to communicate with the interior of the inner catheter. Typically the tip is secured in the opening at the distal end of the inner catheter. Optionally, the tip may be comprised of a radiopaque material.

The inner catheter is provided with a position indicator mark at the location on the inner catheter disposed at the proximal end of the outer catheter when the tip of the inner catheter sealingly engages the distal end of the outer catheter.

With the proximal surface of the tip engaging the distal end of the outer catheter, the outer catheter with the inner catheter disposed therein can be advanced through the upper respiratory system of the patient without contaminating the outer surface of the inner catheter. Thereafter, the inner catheter is advanced relative to the outer catheter and any mucous accumulated in the aperture through the tip thereof is flushed out prior to advancement of the tip into a wedging position in a bronchiole of the patient.

In another aspect of the present invention, the inner catheter comprises a second closure means for facilitating and sustaining wedging of the distal end of the catheter into a bronchiole of the patient. In the embodiment of the invention disclosed herein, such a second closure means takes the form of a tip at the distal end of the inner catheter having a lead surface that comprises a smoothly curving dome that terminates at the outer lateral periphery of the tip. Centrally formed in the dome is an aperture therethrough communicating with the interior of the inner catheter. The outer lateral periphery of the tip has a

diameter larger than the outer surface of the inner catheter.

The radially symmetric shape of the dome permits the tip to advance into a bronchiole and easily engage the walls thereof about the full lateral periphery. Thereafter, de-wedging of the tip from that bronchiole is resisted by the enlarged lateral periphery of the tip relative to the outer surface of the inner catheter. That lateral periphery affords enhanced purchase on the tip by the tissue of the bronchiole wall, much in the manner in which an atraumatic barb resists removal. Nevertheless, the enlarged lateral periphery of the tip is rounded in shape so as to reduce trauma to tissue in the bronchiole wall during the process.

Typically, the inner catheter comprises a single lumen so sized as to permit the infusion and aspiration of a fluid therethrough. Alternatively, however, the inner catheter can comprise a first lumen so sized as to permit such infusion and aspiration, as well as a second lumen having a size relatively smaller than that of the first lumen and being capable of transmitting a gas between the distal and the proximal ends of the inner catheter.

Under such circumstances, the inner catheter further comprises a flexible cuff attached to and encircling the sides of the inner catheter proximal of the distal end thereof. The cuff is selectively inflatable through the second lumen to engage the walls of the bronchiole of the patient. Through the use of such an inflatable cuff, the distal tip of the inner catheter can in effect be wedged in a major bronchia, thereby to permit sampling of a larger lung segment than would be possible, if the distal tip of the catheter were to be advanced into the lung far enough to wedge in a single bronchiole.

In another aspect of the present invention, the outer catheter possesses sufficient structural rigidity as to be

capable, when disposed in the upper respiratory system of the patient, of exhibiting at the distal end thereof a one-to-one rotation about the longitudinal axis thereof relative to the proximal end thereof. Correspondingly, the oxygen insufflation hub of the connector hub assembly located on the proximal end of the outer catheter may be used as a direction indicator designating the direction at which the bend departs from the longitudinal axis of the inner catheter. Through the use of the direction indicator, the bend may be directed toward the desired primary branch of the trachea in order to then advance the outer catheter with the inner catheter disposed therein into a lung of the patient.

Optionally, the catheter disclosed comprises a means for monitoring pressure in the airways of the patient toward the end, for example, of assisting in verifying correct wedging of the distal tip of the inner catheter. Such a means can take the form of a pressure stopcock located between the proximal end of the inner catheter and the means for infusing and aspirating. The pressure stopcock is capable of selectively placing the proximal end of the inner catheter in communication alternatively with the pressure monitor or with the means for infusing and aspirating.

By means of the apparatus and method of the present invention, bronchoalveolar lavage can be performed in an efficient and economical manner using equipment of such low cost as to be disposable. The catheter of the present invention provides the medical practitioner with the capacity to direct the bronchoalveolar lavage catheter toward a preselected one of the lungs of the patient, while protecting the exterior of the catheter which is advanced into the preselected lung from contamination as that catheter is advanced through the upper respiratory system of the patient. In addition, the unique shape of the tip

1 of that sampling catheter facilitates the effecting and
maintenance of desired wedging. Alternatively, wedging can
be accomplished in larger air passageways using an
inflatable cuff located proximal of the distal end of the
catheter.

The present invention also contemplates a method for
performing non-bronchoscopic bronchoalveolar lavage.

BRIEF DESCRIPTION OF THE DRAWINGS

10 In order that the manner in which the above-recited
and other advantages and objects of the invention are
obtained, a more particular description of the invention
briefly described above will be rendered by reference to
specific embodiments thereof which are illustrated in the
15 appended drawings. Understanding that these drawings
depict only typical embodiments of the invention and are
therefore not to be considered limiting of its scope, the
invention will be described with additional specificity and
detail through the use of the accompanying drawings in
20 which:

Figure 1 is a schematic drawing of a system for
conducting bronchoalveolar lavage using the inventive
bronchoalveolar lavage catheter;

25 Figure 2 is a perspective view of the inventive
bronchoalveolar lavage catheter with the distal ends of the
outer and inner catheter in sealing engagement, and
illustrating the connector hub assembly with cap attached;

30 Figure 3 is a perspective view of the bronchoalveolar
lavage catheter shown in Figure 2 with the distal end of
the inner catheter advanced out of the distal end of the
outer catheter, and illustrating the connector hub assembly
connected to a supply of oxygen;

Figure 4 is a perspective detailed view of the distal
ends of the inner and outer catheters and the tip of the

inner catheter of the bronchoalveolar lavage catheter shown in Figure 2;

Figure 5 is a cross-sectional view of the tip of the bronchoalveolar lavage catheter shown in Figure 4 and taken along section line 5-5 shown therein;

Figure 6 is a cross-sectional view of the tip of the bronchoalveolar lavage catheter shown in Figure 4 with the distal end of the inner catheter advanced out of the distal end of the outer catheter, and with oxygen passing from the passageway between the outer catheter and the inner catheter out;

Figures 7A through 7D are a sequence of schematic illustrations of a method for inserting and directing the inner catheter of the bronchoalveolar lavage catheter of Figure 2 into a preselected lung of the patient, wedging the distal tip of the inner catheter in a bronchiole in that lung, and supplying oxygen to the lungs;

Figure 8 is a schematic illustration of a system for conducting bronchoalveolar lavage using a second embodiment of an inventive bronchoalveolar lavage catheter;

Figure 9 is a detailed perspective view of the tip of the inner catheter illustrated in Figure 8;

Figure 10 is a cross-sectional view of the tip of the bronchoalveolar lavage catheter illustrated in Figure 8 taken along section lines 10-10 shown therein;

Figure 11 is a perspective view of the tip of the bronchoalveolar lavage catheter shown in Figure 9 with the cuff on an exterior surface thereof inflated to engage the walls of the bronchi of the patient;

Figure 12 is a cross-section view of the tip of the second embodiment of a bronchoalveolar lavage catheter shown in Figure 11 taken along section line 12-12 shown therein; and

Figure 13 is a cross-section view of the connector hub assembly taken along section line 13-13 of Figure 2.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1 illustrates the environment in which the inventive bronchoalveolar lavage catheter is employed in relation to a patient 10 intubated with an endotracheal tube 12. Although intubation is not required in order to perform bronchoalveolar lavage with the inventive catheter disclosed herein, intubation may be employed expressly for the purpose of facilitating the procedure of bronchoalveolar lavage. Generally, however, intubation is undertaken in order to provide ongoing mechanical ventilation of a patient.

As seen in Figure 1, endotracheal tube 12 extends through the mouth 14 and the trachea 16 of the upper respiratory system of patient 10, terminating in a distal end 18 well above the point 20 at the first bifurcation of trachea 16 into the right lung 22 through the right mainstem bronchus 24 and into the left lung 26 through the left mainstem bronchus 28. Typical sub-branchings of the mainstem bronchus are shown in Figure 1 for illustrative purposes in relation to the sub-branching of left mainstem bronchus 24 into left lung 26.

Distal end 18 of endotracheal tube 12 is provided with a balloon 30 which, when inflated, engages the walls of trachea 16 to facilitate mechanical ventilation of patient 10 through a Y-connector 32 coupled to a standard endotracheal tube adapter 34 at the proximal end 36 of endotracheal tube 12. Air from the ventilating apparatus for patient 10 enters endotracheal tube 12 through a first leg 38 of Y-connector 32, as indicated in Figure 1 by arrow A₁. Correspondingly, air is returned to the ventilating apparatus from patient 10 through a second leg 40 of Y-connector 32, as shown in Figure 1 by arrow A₂.

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An elbow coupling 42 connects endotracheal tube adapter 34 with Y-connector 32 and is provided at a point on the outer radius thereof with a bronchoalveolar lavage catheter port 44 through which a bronchoalveolar lavage catheter can be entered into endotracheal tube 12 and advanced therethrough into a preselected lung of patient 10 without losing the positive end expiratory pressure (PEEP) often required during mechanical ventilation.

It must be emphasized that use of the inventive bronchoalveolar lavage catheter disclosed herein is not limited to use with patients undergoing mechanical ventilation, or even patients in whom intubation with an endotracheal tube has occurred. In addition, as will be apparent subsequently, bronchoalveolar lavage can be conducted with the inventive bronchoalveolar lavage catheter through the nasal passages 45 of patient 10, rather than through the mouth 14 thereof.

As illustrated in Figure 1, bronchoalveolar lavage is to be performed on a portion of left lung 26 of patient 10. In the process, a sterile fluid from a reservoir 46 thereof is infused into individual aliquots using a syringe 48. The fluid of each infusion is then aspirated using either syringe 48 or the wall vacuum in the medical institution in which the bronchoalveolar lavage is conducted. Advantageously, the procedure of bronchoalveolar lavage and in particular the proper wedging of the distal tip of the inventive bronchoalveolar lavage catheter into a bronchiole in left lung 26 of patient 10 is facilitated through the monitoring of air passageway pressures at the distal end of the bronchoalveolar lavage catheter. Toward this end, an air passageway monitor 50 is illustrated having either or both a cathode ray tube display or visual printout.

One embodiment of a bronchoalveolar lavage catheter 60 incorporating teachings of the present invention is illustrated in Figure 1 coupling reservoir 46, syringe 48,

and air passageway pressure monitor 50 through endotracheal tube 12 to left lung 26 of patient 10. Bronchoalveolar lavage catheter 60 is an assembly of subcomponents functioning together for the purpose stated. Nevertheless, it will be understood from the disclosure which follows that some or all of the components thereof may be eliminated from bronchoalveolar lavage catheter 60, while yet incorporating some teachings of the present invention. As shown in Figure 1, bronchoalveolar lavage catheter 60 includes an inner sampling catheter 62 having a distal end 63 and a proximal end 64 so sized and configured as to be capable of extending from a distal bronchiole in left lung 26 of patient 10 through the upper respiratory system to a connection to external patient 10.

According to one aspect of the present invention, at proximal end 64 of sampling catheter 62, means are provided for infusing and aspirating fluid through sampling catheter 62 into the lung of a patient. As shown by way of example and not limitation, a sampling stopcock 66 is coupled to proximal end 64 of sampling catheter 62. Sampling catheter 66 is capable of connection to reservoir 46 and to syringe 48 in such a manner as to selectively place syringe 48 alternately in communication with reservoir 46 or with proximal end 64 of sampling catheter 62.

In another aspect of the inventive bronchoalveolar lavage catheter, means are provided for monitoring pressure in the airways of patient 10. As shown by way of example and not limitation, in Figure 1 a pressure stopcock 68 is located between proximal end 64 of sampling catheter 62 and sampling stopcock 66. Pressure stopcock 68 is capable of selectively placing proximal end 64 of sampling catheter 62 in communication alternately with air passageway pressure monitor 50 or with sampling stopcock 66. In the latter condition, it is impossible to infuse and aspirate fluid

1 from reservoir 46 through sampling catheter 62. When the
process of infusion and aspiration is not ongoing, the
placement of air passageway pressure monitor 50 in
communication with sampling catheter 62 by the appropriate
5 manipulation of pressure stopcock 68 enables a medical
practitioner to evaluate the air pressure patterns in the
air passageways of patient 10 distal of the tip of distal
end 70 of sampling catheter 62, thereby to verify correct
wedging of the tip of distal end 70 of sampling catheter 62
10 in a bronchiole of patient 10.

In yet another aspect of the present invention,
bronchoalveolar lavage catheter 60 includes a means for
directing distal end 70 of sampling catheter 62 into a
preselected lung of patient 10, while also protecting the
outside of sampling catheter 62 from contamination during
15 the advancement of distal end 70 of sampling catheter 62
through the upper respiratory system of patient 10. As
shown by way of example and not limitation, bronchoalveolar
lavage catheter 60 comprises an elongated outer catheter or
insertion sheath 72, having a proximal end 73 and a distal
20 end 74, so sized and configured as to encircle sampling
catheter 62 and to be capable of extending from a location
below the point 20 at the first bifurcation of trachea 16
through the upper respiratory system of patient 10.

The structure of insertion sheath 72 and interaction
25 thereof with sampling catheter 62 during the process of
conducting bronchoalveolar lavage with bronchoalveolar
lavage catheter 60 will be more clearly appreciated by
reference first to Figure 2. There, sampling catheter 62
is disposed within insertion sheath 72 with the tip 75 of
30 sampling catheter 62 at distal end 74 of insertion
sheath 72. Although not seen in this figure, sampling
catheter 62 is disposed within insertion sheath 72 in such
way that a passageway 76 is formed between sampling
catheter 62 and insertion sheath 72. Connected to the
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1 proximal end of insertion sheath 72, and in communication
with the passageway 76, may be means for allowing oxygen
insufflation during the bronchoalveolar lavage process, an
important aspect within the scope of the present invention.
5 In the preferred embodiment within the scope of the present
invention, the means for allowing oxygen insufflation
comprises a connector hub assembly 77, which is connected
to proximal end 73 of insertion sheath 72 and is in gaseous
communication with the passageway 76. Connector hub
10 assembly 77 and passageway 76 can be best seen in
Figure 13, a cross section of the connector hub assembly
taken along line 13-13 of Figure 2.

As can be seen in Figure 13, the connector hub
assembly 77 is comprised of an oxygen insufflation hub 78
15 and a sealing hub 79. Oxygen insufflation hub 78 is in
communication at one end thereof with passageway 76, and is
couplable at the other end thereof with either a supply of
oxygen 80 or a cap 85. Oxygen can be passed from the
supply of oxygen 80, through oxygen insufflation hub 78,
20 through passageway 76, and into the lungs.

Sealing hub 79 is in communication at one end thereof
with passageway 76, and at the other end thereof with a
protection means 81 for sealing passageway 76 at proximal
end 73 of insertion sheath 72. Protection means 81
25 encircles said sampling catheter 62 tightly at the point
where sampling catheter 62 passes through sealing hub 79 of
connector hub assembly 77, thereby forming a seal around
proximal end 73 of insertion sheath 72 such that oxygen
entering passageway 76 from oxygen insufflation hub 78 can
only pass from connector hub assembly 77 in one direction,
30 that being towards the trachea of the user.

In the preferred embodiment, protection means 81 is
comprised of a silicone washer which is of about the same
diameter or slightly smaller than the diameter of sampling
catheter 62. The silicone washer fits snugly around
35

sampling catheter 62, thereby forming a seal over passageway 76.

As can be seen in Figure 13, in the preferred embodiment within the scope of the present invention, oxygen insufflation hub 78 is formed of a luer lock port 82. When the user wishes to connect an oxygen supply to the oxygen insufflation hub, a male luer slip fitting 83 forming the end of an oxygen supply tube 84 may be inserted into the luer lock port 82 in order to pass oxygen from the oxygen supply into the passageway 76, and out distal end 74 of insertion sheath 72. When oxygen is not being supplied, that is, when no oxygen supply tube 84 is connected to oxygen insufflation hub 78, a cap 85 is used to cover and seal oxygen insufflation hub 78.

It can be appreciated that supplemental oxygen will not be needed in every use of the bronchoalveolar lavage catheter of the present invention. Oxygen insufflation will be used only in those cases where the patient is more susceptible because of his or her health to suffering from a desaturation of the lungs which may occur during the bronchoalveolar lavage procedure. For those procedures where supplemental oxygen is not needed, oxygen insufflation hub 78 will be covered with cap 85.

It is also important to note that the capability of the present invention to supply oxygen during the bronchoalveolar lavage procedure is a significant improvement over the prior art. In bronchoscopy, supplemental oxygen cannot be delivered safely to the lungs because on a bronchoscope, all channels terminate at the distal tip. Therefore, when the bronchoscope is wedged, all oxygen passes out of the distal tip into a single lung segment, thereby creating a danger of blowing out the lung and causing a pneumothorax. Providing air to the upper airways, as is possible with the present invention, is not possible with any current bronchoscopes.

1 The ability of bronchoalveolar lavage catheter 60 to
effect bronchoalveolar lavage in a preselected lung of
patient 10 is dependent both upon the structure of distal
end 74 of insertion sheath 72 and upon the material of
5 which insertion sheath 72 is comprised.

Referring once again to Figure 2, distal end 74 of
insertion sheath 72 is displaced at a predetermined bend
angle B to the longitudinal axis of insertion sheath 72.
The oxygen insufflation hub 78 may be used as a direction
10 indicator for insertion sheath 72 if it is constructed to
project from insertion sheath 72 in the same radial
direction as the radial direction at which distal end 74A
of insertion sheath 72 departs from the longitudinal axis
thereof.

15 Insertion sheath 72 is comprised of a relatively rigid
material, such as ethyl vinyl acetate. In this manner,
insertion sheath 72 will by design possess sufficient
structural rigidity as to be capable, when disposed in the
warm, upper respiratory system of patient 10, of
20 nevertheless exhibiting at distal end 74 one-to-one
rotation about the longitudinal axis of insertion sheath 72
relative to proximal end 73 thereof. In this manner, when
insertion sheath 72 is disposed in the upper respiratory
system of patient 10, as shown in Figure 1, the rotation of
25 proximal end 73 of insertion sheath 72 about the
longitudinal axis thereof will result in an identical
rotation of distal end 74 of insertion sheath 72 about the
longitudinal axis thereof. Oxygen insufflation hub 78
outside the body of patient 10 will at all times be
30 oriented in the radial direction at which distal end 74
departs from the longitudinal axis of insertion sheath 72,
thereby affording information to a medical practitioner
about the direction of distal end 74 of insertion sheath 72
inside the body of patient 10. By utilizing this feature
35 of bronchoalveolar lavage catheter 60, it will be seen

subsequently that sampling catheter 62 can be advanced with certainty into a preselected lung of patient 10.

A position indicator mark 86 is provided on sampling catheter 62 at the location thereupon which is disposed at proximal end 73 of insertion sheath 72 when tip 75 of sampling catheter 62 is located at distal end 74 of insertion sheath 72. As will be discussed in further detail subsequently, in this relative position of sampling catheter 62 and insertion sheath 72, tip 75 sealingly engages distal end 74 of insertion sheath 72.

Insertion sheath 72 and sampling catheter 62 are relatively sized so that sampling catheter 62 can slide freely within insertion sheath 72. Thus, as shown in Figure 3, sampling catheter 62 can be advanced into and through insertion sheath 72, so that tip 75 moves away from distal end 74 of insertion sheath 72 a distance D_1 , revealing distal end 63 of sampling catheter 62. Correspondingly, position indicator mark 86 is advanced into proximal end 73 of insertion sheath 72 by distance D_2 equal to the distance D_1 by which distal end 63 of sampling catheter 62 advances out of distal end 74 of insertion sheath 72. The initial direction in which distal end 63 of sampling catheter 62 advances from insertion sheath 72 is determined by the orientation of the bend at distal end 74 of insertion sheath 72.

In use, insertion sheath 72 is disposed in the upper respiratory system of patient 10, and insertion sheath 72 is rotated about the axis thereof to orient direction indicator 78 and distal end 74 of insertion sheath 72 toward a preselected one of lungs 22, 26. Then sampling catheter 62 is advanced out of insertion sheath 72 in the manner illustrated in Figure 3. Doing so necessarily results in distal end 63 of sampling catheter 62 advancing into the same preselected lung. Thereafter, distal end 63 of sampling catheter 62, which desirably is more pliable

than that of insertion sheath 72, is able to advance despite its pliable structure into the preselected lung.

According to another aspect of the present invention, sampling catheter 62 comprises a first closure means located at distal end 70 thereof for sealing distal end 74 of insertion sheath 72 when insertion sheath 72 is disposed encircling sampling catheter 62 with distal end 70 of sampling catheter 62 at distal end 74 of insertion sheath 72. This is the relative positioning of sampling catheter 62 and insertion sheath 72 shown in Figure 2 with position indicators mark 82 being located just at the terminus of proximal end 73 of insertion sheath 72. The first closure means associated with inner catheter 62 is best appreciated, by way of example and not limitation, by reference to the detailed view of tip 75 shown in perspective in Figure 4 and in cross-section in Figures 5 and 6. In the cross-section of Figure 5, tip 75 is shown making sealing engagement with distal end 74 of insertion sheath 72, while in Figure 6, sampling catheter 62 has been advanced relative to insertion sheath 72 in the manner illustrated in Figure 3, so as to separate tip 75 from distal end 74 of insertion sheath 72.

Tip 75 comprises a radially symmetrical insert secured in distal end 70 of sampling catheter 62. Tip 75 comprises a head portion 102 and a stem portion 104 which is received within and secured to the bore of the lumen 106 centrally formed in sampling catheter 62. Tip 75 may be comprised of a radiopaque material to render it locatable by x-ray or fluoroscopic examination when inside the body of patient 10.

Centrally formed through tip 75 is an aperture 108 which communicates with lumen 106 at the interior of sampling catheter 62. Head portion 102 of tip 75 has an outer lateral periphery 110 which is larger in diameter than the outer surface 112 of sampling catheter 62.

Between outer lateral periphery 110 of tip 75 and outer surface 112 of sampling catheter 62, head portion 102 of tip 75 defines an annular proximal surface 114 which encircles and is normal to outer surface 112 of sampling catheter 62 when tip 75 is secured in distal end 70 of sampling catheter 62.

When insertion sheath 72 and sampling catheter 62 are in the relative positions illustrated in Figure 2, annular proximal surface 114 of tip 75 engages lateral surface 116 (Figures 5 and 6) at the terminus of distal end 74 of insertion sheath 72. Under such conditions, insertion sheath 72 with sampling catheter 62 disposed therein can be advanced through the upper respiratory system of patient 10, while protecting outer surface 112 of sampling catheter 62 from contamination by micro-organisms residing the upper respiratory system. Sampling catheter 62 is advanced out of insertion sheath 72, exposing outer surface 112 of sampling catheter 62 to ambient contaminations only after distal end 74 of insertion sheath 72 has been rotated toward preselected lung and has been advanced beyond the point 20 at the first bifurcation of trachea 16. At this location in the respiratory system of patient 10 the chances that micro-organisms inhabiting the upper respiratory system will attach to outer surface 112 of sampling catheter 62 are substantially reduced. This contributes to more accuracy in the sampling recovered through sampling catheter 62.

According to another aspect of the present invention, sampling catheter 62 comprises a second closure means located at distal end 70 thereof for facilitating wedging of distal end 70 of sampling catheter 62 into a bronchiole of patient 10. As also shown, by way of example and not limitation, in Figures 4-6 tip 75 of sampling catheter 62 is provided with a lead surface 118 comprising a smoothly curved dome terminating at outer lateral periphery 110 of

1 tip 75. Aperture 108 is centrally formed in the dome of
lead surface 118 so as to communicate with lumen 106 at the
interior of sampling catheter 106.

3 During the advancement of sampling catheter 62 out of
5 insertion sheath 72 and into the preselected one of
lungs 22, 24, the size of the air passage through which
tip 75 is advanced gradually decreases until lead
surface 118 of tip 75 wedges within the walls of a single
10 bronchiole. The shape of lead surface 118 assists in the
process of initial wedging by continuing to deflect tip 75
away from the wall of the air passageway into which
sampling catheter 62 is being advanced, until the walls of
that air passageway uniformly surround and close upon the
15 circumference of tip 72 at outer lateral periphery 110
thereof. The smooth shape of lead surface 118 has the
effect of minimizing trauma as wedging is actually
affected.

Thereafter, the mushroom-shaped cross-section of
tip 75, and in particular, the overhang at outer lateral
20 periphery 110 thereof, prevents the inadvertent withdrawal
of tip 75 from its wedged position. Tissue from the wall
of the air passageway in which tip 75 is wedged, presses
about the full circumference of outer lateral
periphery 110. The tissue of the air passageway walls on
25 the same side of outer lateral periphery 110 as proximal
surface 114 becomes disposed radially inwardly of outer
lateral periphery 110 behind head portion 102 of tip 75.
This tissue tends desirably to hold head portion 102 in its
wedging position, and the infusion and aspiration of
30 sampling fluid as required for bronchoalveolar lavage can
thereafter be safely and reliably undertaken.

The steps for utilizing bronchoalveolar lavage
catheter 60 will be reviewed with reference to the series
of Figures 7A through 7D. Insertion sheath 72 with
35 sampling catheter 62 disposed therein in the manner shown

in Figure 2 is introduced into endotracheal tube 12 through an appropriate coupling, such as elbow coupling 42 and bronchoalveolar lavage catheter access port 44. The assembly of insertion sheath 74 with sampling catheter 62 therein is advanced through the upper respiratory system of patient 10 and to distal end 18 of endotracheal tube 12. This is the position of distal end 74 of insertion sheath 72 shown in solid lines in Figure 7A.

Thereafter, the assembly of insertion sheath 72 with sampling catheter 62 therein is advanced out of distal end 18 of endotracheal tube 12 into trachea 16 of the upper respiratory system of patient 10. The advancement of the assembly is terminated above point 20 at the first bifurcation of trachea 16. This is the position of insertion sheath 72 shown in dashed lines in Figure 7A. As thus shown, the bend at distal end 74 of insertion sheath 72 is oriented toward right mainstem bronchus 24 leading into right lung 22 (not shown). Were sampling catheter 62 to be advanced out of distal end 74 of insertion sheath 72 with distal end 74 of insertion sheath 72 disposed in the orientation illustrated in dashed lines in Figure 7A, then tip 75 of sampling catheter 62 would advance into right mainstem bronchus 24 and ultimately into right lung 22 (not shown) of patient 10. Nevertheless, due to the structure of insertion sheath 72 in particular, it is possible in the alternative with a high degree of reliability to reorient tip 75 of sampling catheter 62 into left mainstem bronchus 28, so that tip 75 ultimately wedges into a bronchiole in left lung 26 (not shown) of patient 10.

To accomplish this end, it is only necessary to rotate proximal end 73 (Figures 2 and 3) of insertion sheath 74 outside the body of patient 10 by an appropriate degree. Because of the relative structural rigidity imparted to insertion sheath 72 by the material of which it is

comprised, rotation of proximal end 73 thereof results in a one-to-one rotation of distal end 74 as, for example, illustrated in Figure 7A by arrow R.

The rotation of insertion sheath 72 about the longitudinal axis thereof in the manner illustrated by arrow R in Figure 7A will eventually bring the bend at distal end 74 of insertion sheath 72 to be oriented toward left mainstem bronchus 28, as shown in Figure 7B. In the orientation of distal end 74 of insertion sheath 72 illustrated, the advancement of sampling catheter 62 out of distal end 74 of insertion sheath 72 will direct tip 75 of sampling catheter 62 into left mainstem bronchus 28. Nevertheless, in order to insure this result, it is advisable to further advance the assembly of insertion sheath 72 with sampling catheter 62 somewhat further into the respiratory system of patient 10. In this manner distal end 74 of insertion sheath 72 actually enters left mainstem bronchus 28, assuming for example the position illustrated in Figure 7C. Then sampling catheter 62 is advanced out of distal end 74 of insertion sheath 72.

Until this has occurred, tip 75 effects a sealing engagement with distal end 74 of insertion sheath 72, and the outer surface 112 of sampling catheter 62 is protected from contamination from the upper respiratory system of patient 10. Nevertheless, the outer surface of tip 75 of sampling catheter 62 can still become contaminated, and aperture 108 centrally formed therein can become blocked with contaminated mucous. Accordingly, after full advancement of insertion sheath 72 into the body of patient 10, distal end 63 of sampling catheter 62 is advanced out of distal end 74 of insertion sheath 72 a short distance and a small quantity of fluid 120 from reservoir 46 (Figure 1) is used to flush any plug of contaminated mucous from aperture 108 in tip 75. Fluid 120

passes harmlessly into the bronchioles 122 of patient 10 below tip 75.

Thereafter, sampling catheter 62 is advanced out of insertion sheath 72 into the bronchioles 122 of patient 10 until tip 75 of sampling catheter 62 becomes wedged in a bronchiole, shown, for example, as bronchiole 122a in Figure 7D. Wedging may be verified through the appropriate use of air passageway pressure monitor 50. Longitudinal movement of sampling catheter 62 thereafter is advisedly restrained by suitable means, such as those locatable in bronchoalveolar lavage catheter access port 44 (Figure 1). Thereafter, fluid from reservoir 46 is infused into the position of left lung 26 isolated by the wedging of tip 75 into bronchiole 122a and aspirated using sampling stopcock 66 in combination with syringe 48.

Once the sampling catheter 62 is advanced into a bronchiole, insertion sheath 72 may be withdrawn to a position just above the bifurcation, as shown in Figure 7D. An oxygen supply is then connected to the oxygen insufflation hub 78, and oxygen is passed through passageway 76 and out distal end 74 of insertion sheath 72 into the lungs. At this position above the bifurcation, it does not matter whether insertion sheath 72 is facing towards the right or left main stem bronchus. As oxygen is passed out of distal end 74, turbulence causes the oxygen to swirl and enter both branches of the lungs. Swirling arrows in Figure 7D illustrate the exit path of the oxygen.

Figure 8 illustrates a system for conducting bronchoalveolar lavage using a second embodiment of a bronchoalveolar lavage catheter 130. Structures of bronchoalveolar lavage catheter 130 and the system employed therewith that are identical to corresponding structures associated with bronchoalveolar lavage catheter 60 or the system employed therewith will be referred to by identical reference figures. Accordingly, only the differences

1 between these two embodiments of a bronchoalveolar lavage catheter will be discussed in detail.

5 In Figure 8, bronchoalveolar lavage catheter 130 is shown entered into left lung 26 of patient 10 by way of nasal passages 45 and trachea 16 in the upper respiratory system thereof. While the process of conducting bronchoalveolar lavage catheter could, as illustrated in Figure 1, be conducted through an endotracheal tube, thereby permitting patient 10 to be mechanically ventilated, in Figure 8 bronchoalveolar lavage catheter 130 is employed without any additional medical equipment. Bronchoalveolar lavage catheter 130 comprises a sampling catheter 62 with a tip 75 at distal end 63 thereof housed and slidable within an insertion sheath 72 having a bend at the distal end 74 thereof that departs at a predetermined bend angle from the longitudinal axis. The proximal end 74 of sampling catheter 62 is coupled through a pressure stopcock 68 to a sampling stopcock 66, both of which perform functions substantially similar to those already described in relation to bronchoalveolar lavage catheter 60 of Figure 1.

15 In contrast therewith, however, bronchoalveolar lavage catheter 130 comprises a balloon inflation syringe 132 and, correspondingly, a flexible cuff 134 shown in additional detail in Figure 9 as being attached to and encircling outer surface 112 of sampling catheter 62 proximal of tip 75 at distal end 63 thereof.

25 As more clearly understood by reference to the cross-section of Figure 10, sampling catheter 62 of bronchoalveolar lavage catheter 130 comprises a first lumen 136 so sized as to permit the infusion and aspiration of a fluid from reservoir 46 through sampling catheter 62. In addition, however, sampling catheter 62 comprises a second lumen 138 having a size relatively smaller than that of first lumen 136 and being capable of transmitting a gas

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between balloon inflation syringe 132 and proximal end 64 of sampling catheter 62. Tip 75 of sampling catheter 62 is secured in the end of first lumen 136 in such a manner that proximal surface 114 of tip 75 closes distal end 140 of second lumen 138. Flexible cuff 134 is a generally cylindrical sheet secured at each periphery 142 thereof to outer surface 112 of sampling catheter 62. This defines between flexible cuff 134 and outer surface 112 an annular inflation space 144. An inflation aperture 146 communicates between second lumen 138 and inflation space 144.

Flexible cuff 134 is thus inflatable utilizing balloon inflation syringe 132 to force a gas through second lumen 138 and inflation aperture 146 into inflation space 144. The result as illustrated in Figures 11 and 12 is the inflation of flexible cuff 134 into engagement with the walls 148 of a bronchiole 122b of patient 10 which is larger in diameter than bronchiole 122a (Figure 7D) in which tip 75 of sampling catheter 62 could become. Under such conditions, a larger section of a preselected one of lungs 22, 26 of patient 10 can be subjected to bronchoalveolar lavage sampling.

The presence of flexible cuff 134 on outer surface 112 of sampling catheter 62 affects the relative sizing in sampling catheter 62 and in insertion sheath 72. Without any inflation cuff such as flexible cuff 134, insertion sheath 72 might typically be a sixteen French catheter and sampling catheter 62 a twelve French catheter. Additional clearance between these two structures is required, however, if sampling catheter 62 with flexible cuff 134 secured to the exterior thereof is to be moveable freely and longitudinally within insertion sheath 72. Accordingly, if insertion sheath 72 is a sixteen French catheter, sampling catheter 62 should be reduced in size to that of a ten French catheter. Alternatively, if

1 sampling catheter 62 is a twelve French catheter, insertion
sheath 72 should be increased in size to that of
an eighteen French catheter.

5 The inventive bronchoalveolar lavage catheters
disclosed are substantial advances towards improving the
accuracy and ease of diagnosing inflammations and other
abnormalities of the lungs. The practitioner utilizing the
inventive bronchoalveolar lavage catheter can with
10 reliability sample from either the left or the right lung
and do so in the manner which minimizes contamination by
the upper respiratory system, either of the equipment
utilized at the sampling site, or of the lower respiratory
system of the patient. The ease of catheter placement
15 facilitated by the inventive bronchoalveolar lavage
catheter eliminates the need in conducting bronchoalveolar
lavage to resort to costly bronchoscopic techniques.
Accordingly, the inventive bronchoalveolar lavage catheter
is so inexpensive to produce as to render it disposable.
20 This obviates the need for expensive equipment inventories
and costly and time consuming sterilizations between
procedures.

The present invention may be embodied in other
specific forms without departing from its spirit or
essential characteristics. The described embodiments are
25 to be considered in all respects only as illustrative and
not restrictive. The scope of the invention is, therefore,
indicated by the appended claims rather than by the
foregoing description. All changes which come within the
meaning and range of equivalency of the claims are to be
30 embraced within their scope.

What is claimed is:

Claims:

1. An assembly for performing bronchoalveolar lavage, said assembly comprising:

(a) a sampling catheter having a proximal end and a distal end so sized and configured as to extend from a bronchiole in the lung of a patient through the upper respiratory system of the patient;

(b) means located at the proximal end of said sampling catheter for infusing and aspirating fluid through said sampling catheter; and

(c) means for directing the distal end of said sampling catheter into a lung of the patient and for protecting the outside of said sampling catheter from contamination during advancement of said distal end of said sampling catheter through the upper respiratory system of the patient.

2. An assembly as recited in Claim 1, wherein said means for directing and for protecting comprises an elongated insertion sheath having a proximal end and a distal end so sized and configured as to encircle said sampling catheter and to be capable of extending from below the first bifurcation of the trachea of the patient through the upper respiratory system of the patient.

3. An assembly as recited in Claim 2, wherein said insertion sheath possess sufficient structural rigidity as to be capable, when disposed in the upper respiratory system of the patient, of exhibiting at the distal end thereof one-to-one rotation about the longitudinal axis thereof relative to the proximal end thereof.

4. An assembly as recited in Claim 3, wherein the distal end of said insertion sheath is displaced at a predetermined bend angle to the longitudinal axis of said insertion sheath.

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5. An assembly as recited in Claim 4, wherein the proximal end of said insertion sheath is provided with a direction indicator designating the radial direction at which said distal end of said insertion sheath departs from the longitudinal axis thereof.

6. An assembly as recited in Claim 3, wherein said insertion sheath is comprised of ethyl vinyl acetate.

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7. An assembly as recited in Claim 2, wherein said sampling catheter comprises a tip at the distal end thereof, the outer lateral periphery of said tip having a diameter larger than the outer surface of said sampling catheter, said tip having a proximal surface between said outer lateral periphery and said outer surface of said sampling catheter capable of sealingly engaging said distal end of said insertion sheath when said insertion sheath is disposed encircling said sampling catheter with said distal end of said sampling catheter at said distal end of said insertion sheath.

8. An assembly as recited in Claim 7, wherein said sampling catheter is provided with a position indicator mark at the location on said sampling catheter disposed at said proximal end of said insertion sheath when said tip of said sampling catheter sealingly engages said distal end of said insertion sheath.

9. An assembly as recited in Claim 7, wherein the surface of said tip opposite from said proximal surface thereof defines a lead surface of said tip, and wherein said lead surface of said tip comprises a smoothly curving dome terminating at said outer lateral periphery of said

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tip, thereby to facilitate wedging of said distal end of said sampling catheter into a bronchiole of the patient.

10. An assembly as recited in Claim 2, wherein said sampling catheter comprises a tip at the distal end thereof, said tip having a lead surface comprising a smoothly curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said sampling catheter into a bronchiole of a patient.

11. An assembly as recited in Claim 10, wherein said tip has a diameter larger than the outer surface of said sampling catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface of said sampling catheter which sustains wedging of the distal end of said sampling catheter in a bronchiole of a patient.

12. An assembly as recited in Claim 11, wherein said tip is comprised of a soft, biocompatible material, thereby to minimize trauma to patient tissue due to wedging of said distal end of said sampling catheter into a bronchiole of the patient.

13. An assembly as recited in Claim 11, wherein said outer lateral periphery of said tip has a diameter larger than the diameter of the outer surface of said sampling catheter.

14. An assembly as recited in Claim 13, wherein the surface between said outer lateral periphery of said tip and said outer surface of said sampling catheter defines a proximal surface of said tip, and said proximal surface of said tip is capable of sealingly engaging said distal end

1 of said insertion sheath when said insertion sheath is
disposed encircling said sampling catheter with said distal
end of said sampling catheter at said distal end of said
insertion sheath.

5

15. An assembly as recited in Claim 14, wherein said
sampling catheter is provided with a position indicator
mark at the location on said sampling catheter disposed at
said proximal end of said insertion sheath when said tip of
10 said sampling catheter sealingly engages said distal end of
said insertion sheath.

16. An assembly as recited in Claim 1, wherein said
sampling catheter comprises a flexible cuff attached to and
15 encircling the sides of said sampling catheter proximal of
said distal end thereof, said cuff being selectively
inflatable through said sampling catheter to engage the
walls of a bronchiole of the patient.

20 17. An assembly as recited in Claim 1, wherein said
means for infusing and for aspirating comprises a sampling
stopcock located at said proximal end of said sampling
catheter, said sampling stopcock being connectable to a
reservoir of a fluid and to a syringe for infusing the
25 fluid through the sampling catheter.

18. An assembly as recited in Claim 17, wherein said
sampling stopcock is capable of selectively placing the
syringe alternately in communication with the reservoir of
30 fluid or with said proximal end of said sampling catheter.

19. A catheter for performing bronchoalveolar lavage,
said catheter comprising:

(a) an outer catheter having a proximal end and
35 a distal end so sized and configured as to extend from

1 below the first bifurcation of the trachea of a
patient through the upper respiratory system of the
patient;

3 (b) an inner catheter having a proximal end and
5 a distal end disposable inside said outer catheter and
being so sized and configured as to extend from a
bronchiole in the lung of a patient through the upper
respiratory system of the patient; and

10 (c) means located at the proximal end of said
inner catheter for infusing and aspirating fluid
through said inner catheter.

20. A catheter as recited in Claim 19, wherein said
inner catheter comprises a first closure means located at
15 said distal end of said inner catheter for sealing the
distal end of said outer catheter when said outer catheter
is disposed encircling said inner catheter with said distal
end of said inner catheter at said distal end of said outer
catheter.

20 21. A catheter as recited in Claim 20, wherein said
first closure means comprises a tip at the distal end of
said inner catheter, said tip having an outer lateral
periphery larger in diameter than the outer surface of said
25 inner catheter, and said tip having a proximal surface
between said outer lateral periphery and said outer surface
of said inner catheter capable of sealingly engaging said
distal end of said outer catheter when said outer catheter
is disposed encircling said inner catheter with said distal
30 end of said inner catheter at said distal end of said outer
catheter.

22. A catheter as recited in Claim 21, wherein said
tip is secured in the opening at said distal end of said
35 inner catheter.

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23. A catheter as recited in Claim 19, wherein said inner catheter comprises a second closure means for facilitating wedging of said distal end of said inner catheter into a bronchiole of a patient.

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24. A catheter as recited in Claim 23, wherein said second closure means comprises a tip at said distal end of said inner catheter, the lead surface of said tip comprising a smoothly curving dome terminating at the outer lateral periphery of said tip, said dome having formed centrally therethrough an aperture communicating with the interior of said inner catheter.

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25. A catheter as recited in Claim 24, wherein said tip is secured in the opening at said distal end of said inner catheter.

15

26. A catheter as recited in Claim 19, wherein said inner catheter comprises a tip at the distal end thereof, the outer lateral periphery of said tip having a diameter larger than the outer surface of said inner catheter, said tip having a proximal surface between said outer lateral periphery and said outer surface of said inner catheter capable of sealingly engaging said distal end of said outer catheter when said outer catheter is disposed encircling said inner catheter with said distal end of said inner catheter at said distal end of said outer catheter.

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27. A catheter as recited in Claim 26, wherein said inner catheter is provided with a position indicator mark at the location on said inner catheter disposed at said proximal end of said outer catheter when said tip of said inner catheter sealingly engages said distal end of said outer catheter.

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28. A catheter as recited in Claim 26, wherein the surface of said tip opposite from said proximal surface thereof defines a lead surface of said tip, and wherein
5 said lead surface of said tip comprises a smoothly curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said inner catheter into a bronchiole of said patient.

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29. A catheter as recited in Claim 28, wherein said tip has a diameter larger than the outer surface of said inner catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface of said inner catheter which sustains wedging of the distal
15 end of said inner catheter in a bronchiole of a patient.

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30. A catheter as recited in Claim 19, wherein said inner catheter comprises a tip at the distal end thereof, said tip having a lead surface comprising a smoothly
20 curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said inner catheter into a bronchiole of a patient.

25

31. A catheter as recited in Claim 30, wherein said tip has a diameter larger than the outer surface of said inner catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface of said inner catheter which sustains wedging of the distal
end of said inner catheter in a bronchiole of a patient.

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32. A catheter as recited in Claim 19, wherein said inner catheter comprises a tip secured in the opening at the distal end thereof, said tip having a mushroom-shaped transverse cross-section.

35

1 33. A catheter as recited in Claim 32, wherein the
surface between said outer lateral periphery of said tip
and said outer surface of said inner catheter defines a
proximal surface of said tip, and said proximal surface of
3 said tip is capable of sealingly engaging said distal end
of said outer catheter when said outer catheter is disposed
encircling said inner catheter with said distal end of said
inner catheter at said distal end of said outer catheter.

10 34. A catheter as recited in Claim 33, wherein said
inner catheter is provided with a position indicator mark
at the location on said inner catheter disposed at said
proximal end of said outer catheter when said tip of said
inner catheter sealingly engages said distal end of said
15 outer catheter.

 35. A catheter as recited in Claim 30, wherein said
tip is comprised of a radio-opaque material.

20 36. A catheter as recited in Claim 19, wherein said
inner catheter comprises a single lumen so sized as to
permit the infusion and aspiration of a fluid therethrough.

 37. A catheter as recited in Claim 19, wherein said
25 inner catheter comprises:

 (a) a first lumen so sized as to permit the
infusion and aspiration of a fluid through said inner
catheter; and

 (b) a second lumen having a size relatively
30 smaller than that of said first lumen and being
capable of transmitting a gas between said distal and
said proximal ends of said inner catheter.

 38. A catheter as recited in Claim 37, wherein said
35 inner catheter comprises a flexible cuff attached to and

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1 encircling the sides of said inner catheter proximal of
said distal end thereof, said cuff being selectively
inflatable by a gas passed through said second lumen of
said inner catheter, thereby to engage the walls of a
5 bronchiole of the patient.

39. A catheter as recited in Claim 38, wherein said
inner catheter is a ten French catheter.

10 40. A catheter as recited in Claim 39, wherein said
outer catheter is a sixteen French catheter.

41. A catheter as recited in Claim 39, wherein said
outer catheter comprises an eighteen French catheter.

15 42. A catheter as recited in Claim 41, wherein said
inner catheter comprises a twelve French catheter.

20 43. A catheter as recited in Claim 19, wherein said
inner catheter comprises a flexible cuff attached to and
encircling the sides of said inner catheter proximal of
said distal end thereof, said cuff being selectively
inflatable to engage the walls of a bronchiole of the
patient.

25 44. A catheter as recited in Claim 19, wherein said
inner catheter is comprised of polyvinylchloride.

30 45. A catheter as recited in Claim 19, wherein said
inner catheter comprises a twelve French catheter.

46. A catheter as recited in Claim 44, wherein said
outer catheter is a sixteen French catheter.

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1 47. A catheter as recited in Claim 19, wherein said
outer catheter possess sufficient structural rigidity as to
be capable, when disposed in the upper respiratory system
of the patient, of exhibiting at the distal end thereof
5 one-to-one rotation about the longitudinal axis thereof
relative to the proximal end thereof.

 48. A catheter as recited in Claim 47, wherein the
distal end of said outer catheter is displaced at a
predetermined bend angle to the longitudinal axis of said
10 outer catheter.

 49. A catheter as recited in Claim 48, wherein the
proximal end of said outer catheter is provided with a
direction indicator designating the direction at which said
15 bend at said distal end of said outer catheter departs from
the longitudinal axis thereof.

 50. A catheter as recited in Claim 47, wherein said
20 outer catheter is comprised of ethyl vinyl acetate.

 51. A catheter as recited in Claim 19, wherein said
means for infusing and for aspirating comprises a sampling
stopcock located at said proximal end of said sampling
catheter, said sampling stopcock being connectable to a
25 reservoir of a fluid and to a syringe for infusing the
fluid through the inner catheter.

 52. A catheter as recited in Claim 51, wherein said
30 sampling stopcock is capable of selectively placing the
syringe alternately in communication with the reservoir of
fluid or with said proximal end of said outer catheter.

53. A catheter as recited in Claim 19, further comprising means for monitoring pressure in the airways of the patient.

54. A catheter as recited in Claim 53, wherein said means for monitoring pressure comprises a pressure stopcock located between said proximal end of said inner catheter and said means for infusing and aspirating.

55. A catheter as recited in Claim 54, wherein said pressure stopcock is capable of selectively placing said proximal end of said inner catheter in communication alternatively with a pressure monitor or with said means for infusing and aspirating.

56. A catheter for performing nonbronchoscopic bronchoalveolar lavage, said catheter comprising:

(a) an elongated insertion sheath having a proximal end and a distal end so sized and configured as to extend from below the first bifurcation of the trachea of the patient through the upper respiratory system of the patient, said insertion sheath possessing sufficient rigidity as to be capable, when disposed in the upper respiratory system of a patient, of exhibiting at the distal end thereof one-to-one rotation about the longitudinal axis thereof relative to the proximal end thereof, said distal end of said insertion sheath being displaced at a predetermined bend angle to the longitudinal axis thereof;

(b) a sampling catheter having a proximal end and a distal end disposable inside said outer catheter and being so sized and configured as to extend from a bronchiole of the lung of a patient through the upper respiratory system of the patient;

(c) a closure tip secured in said distal end of said sampling catheter, said closure tip comprising:

1 (i) an outer lateral periphery larger in diameter than the diameter of the outer surface of said sampling catheter;

5 (ii) a proximal surface between said outer lateral periphery thereof and said outer surface of said sampling catheter capable of sealingly engaging said distal end of said insertion sheath when said insertion sheath is disposed encircling said sampling catheter with said distal end of
10 said sampling catheter at said distal end of said insertion sheath;

15 (iii) a lead surface at the opposite end of said closure tip from said proximal surface comprising a smoothly curving dome terminating at said outer lateral periphery of said closure tip, thereby facilitating wedging of said distal end of said sampling catheter into a bronchiole of the patient; and

20 (iv) an aperture centrally formed through said closure tip from said dome to the interior of said sampling catheter; and

25 (d) a sampling stopcock located at the proximal end of said sampling catheter and connectable to a reservoir of a fluid and to a syringe for infusing the fluid through the sampling catheter, said sampling stopcock being capable of selectively placing the syringe alternately in communication with the reservoir of fluid or said proximal end of said sampling catheter.

30 57. A catheter as recited in Claim 56, further comprising a pressure stopcock located between said proximal end of said sampling catheter and said sampling stopcock, said stopcock being capable of selectively
35 placing said proximal end of said sampling catheter in

1 communication alternatively with a pressure monitor or with
said sampling stopcock.

58. A catheter as recited in Claim 56, wherein said
5 sampling catheter comprises a single lumen so sized as to
permit the infusion and aspiration of a fluid therethrough.

59. A catheter as recited in Claim 56, wherein said
sampling catheter comprises:

10 (a) a first lumen so sized as to permit the
infusion and aspiration of a fluid through said
sampling catheter; and

(b) a second lumen having a size relatively
smaller than that of said first lumen and being
15 capable of transmitting a gas between said distal end
said proximal ends of said sampling catheter.

60. A catheter as recited in Claim 59, further
comprising a flexible cuff attached to and encircling the
20 sides of said sampling catheter proximal of said distal end
thereof, said cuff being inflatable by a gas passed through
said second lumen of said sampling catheter, thereby to
engage the walls of a bronchiole of the patient.

25 61. An assembly for performing bronchoalveolar
lavage, said assembly comprising:

(a) a sampling catheter having a proximal end
and a distal end, said sampling catheter so sized and
configured as to be capable of extending from a
30 bronchiole in the lung of a patient through the upper
respiratory system of the patient;

(b) means located at the proximal end of said
sampling catheter for infusing and aspirating fluid
through said sampling catheter;

1 (c) means for directing the distal end of said
sampling catheter into a lung of the patient and for
protecting the outside of said sampling catheter from
contamination during advancement of said distal end of
3 said sampling catheter through the upper respiratory
system of the patient; and

(d) means for allowing oxygen insufflation
during performance of bronchoalveolar lavage.

10 62. An assembly as recited in Claim 61, wherein said
means for allowing oxygen insufflation during performance
of bronchoalveolar lavage comprises a connector hub
assembly connected to said insertion sheath at said
proximal end of said insertion sheath, and in gaseous
15 communication with said passageway formed between said
sampling catheter and said insertion sheath, said connector
hub assembly comprising:

(a) an oxygen insufflation hub communicating at
one end thereof with the passageway formed between
20 said sampling catheter and said insertion sheath, and
couplable at the other end thereof with the supply of
oxygen; and

(b) a sealing hub communicating at one end
thereof with the passageway formed between said
25 sampling catheter and said insertion sheath, and at
the other end thereof with a protection means for
sealing said connector hub assembly, said protection
means encircling said sampling catheter tightly where
said sampling catheter passes through said connector
30 hub assembly, said protection means forming a seal
around said proximal end of said insertion sheath such
that oxygen entering said passageway formed between
said sampling catheter and said insertion sheath from
said oxygen insufflation hub is prevented from
35 escaping in the direction of said sealing hub.

63. A catheter for performing nonbronchoscopic bronchoalveolar lavage, said catheter comprising:

(a) an elongated insertion sheath having a proximal end and a distal end, said elongated sheath so sized and configured as to extend from below the first bifurcation of the trachea of the patient through the upper respiratory system of the patient, said insertion sheath possessing sufficient rigidity as to be capable, when disposed in the upper respiratory system of a patient, of exhibiting at the distal end thereof one-to-one rotation about the longitudinal axis thereof relative to the proximal end thereof, said distal end of said insertion sheath being displaced at a predetermined bend angle to the longitudinal axis thereof;

(b) a sampling catheter having a proximal end and a distal end disposable inside said outer catheter in such way that there is a passageway formed between said sampling catheter and said outer catheter, and being so sized and configured as to extend from a bronchiole of the lung of a patient through the upper respiratory system of the patient;

(c) a closure tip secured in said distal end of said sampling catheter, said closure tip comprising:

(i) an outer lateral periphery larger in diameter than the diameter of the outer surface of said sampling catheter;

(ii) a proximal surface between said outer lateral periphery thereof and said outer surface of said sampling catheter capable of sealingly engaging said distal end of said insertion sheath when said insertion sheath is disposed encircling said sampling catheter with said distal end of

1 said sampling catheter at said distal end of said
insertion sheath;

3 (iii) a lead surface at the opposite end of
said closure tip from said proximal surface
comprising a smoothly curving dome terminating at
said outer lateral periphery of said closure tip,
thereby facilitating wedging of said distal end
of said sampling catheter into a bronchiole of
the patient; and

10 (iv) an aperture centrally formed through
said closure tip from said dome to the interior
of said sampling catheter;

15 (d) a sampling stopcock located at the proximal
end of said sampling catheter and connectable to a
reservoir of a fluid and to a syringe for infusing the
fluid through the sampling catheter, said sampling
stopcock being capable of selectively placing the
syringe alternately in communication with the
reservoir of fluid or said proximal end of said
20 sampling catheter; and

25 (e) a connector hub assembly for allowing oxygen
insufflation during performance of bronchoalveolar
lavage, said connector hub assembly being connected to
said outer catheter at said proximal end of said outer
catheter and in gaseous communication with said
passageway formed between said sampling catheter and
said insertion sheath, said connector hub assembly
comprising:

30 (i) an oxygen insufflation hub
communicating at one end thereof with the
passageway formed between said sampling catheter
and said outer catheter and couplable at the
other end thereof with the supply of oxygen; and

35 (ii) a sealing hub communicating at one end
thereof with the passageway formed between said

1 sampling catheter and said outer catheter and at
the other end thereof with a protection means for
sealing said connector hub assembly, said
5 protection means encircling said sampling
catheter tightly where said sampling catheter
passes through said connector hub assembly, said
protection means forming a seal around said
proximal end of said outer catheter such that
10 oxygen entering said passageway formed between
said sampling catheter and said outer catheter
from said oxygen insufflation hub is prevented
from escaping in the direction of said sealing
hub.

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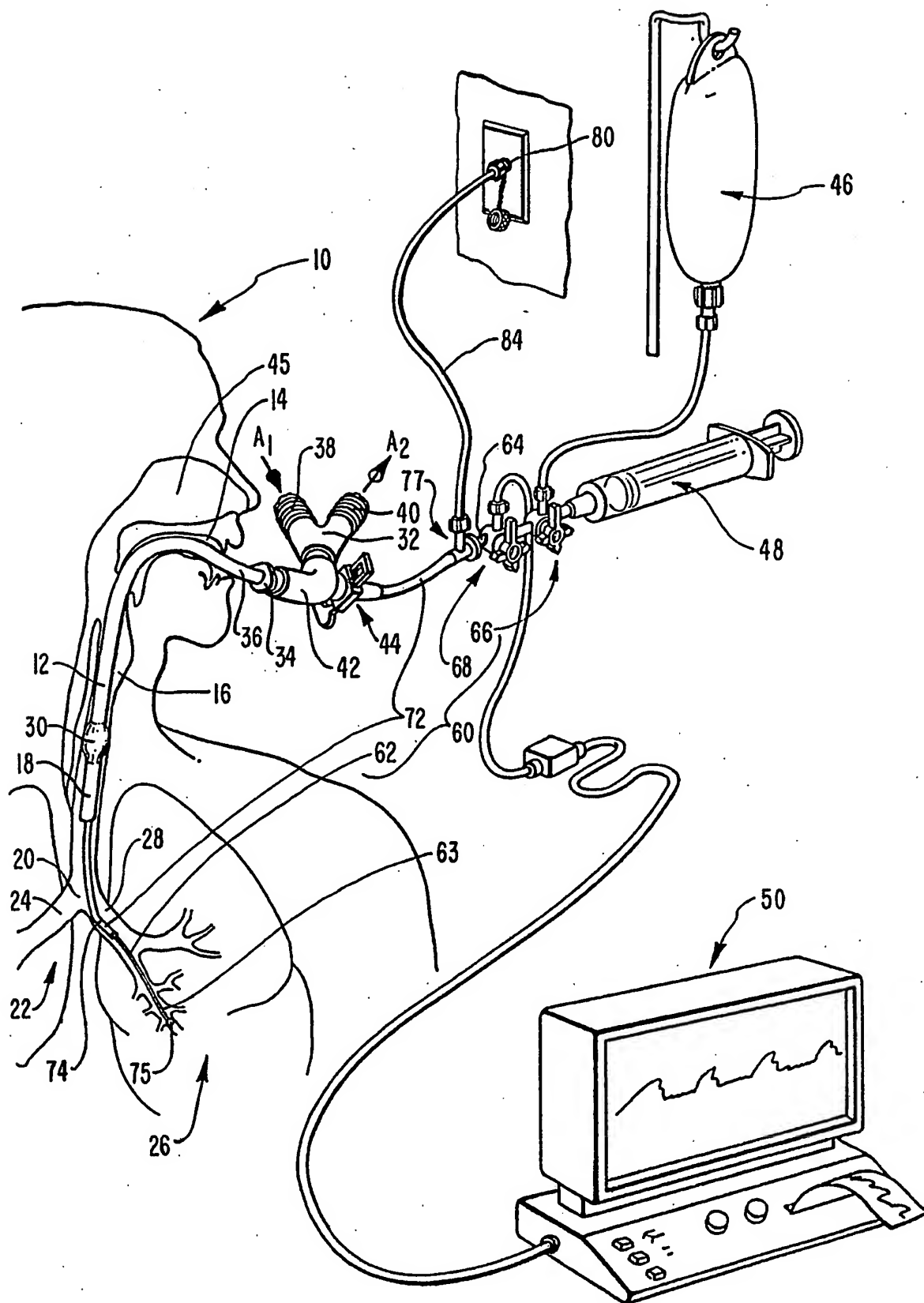


FIG. 1

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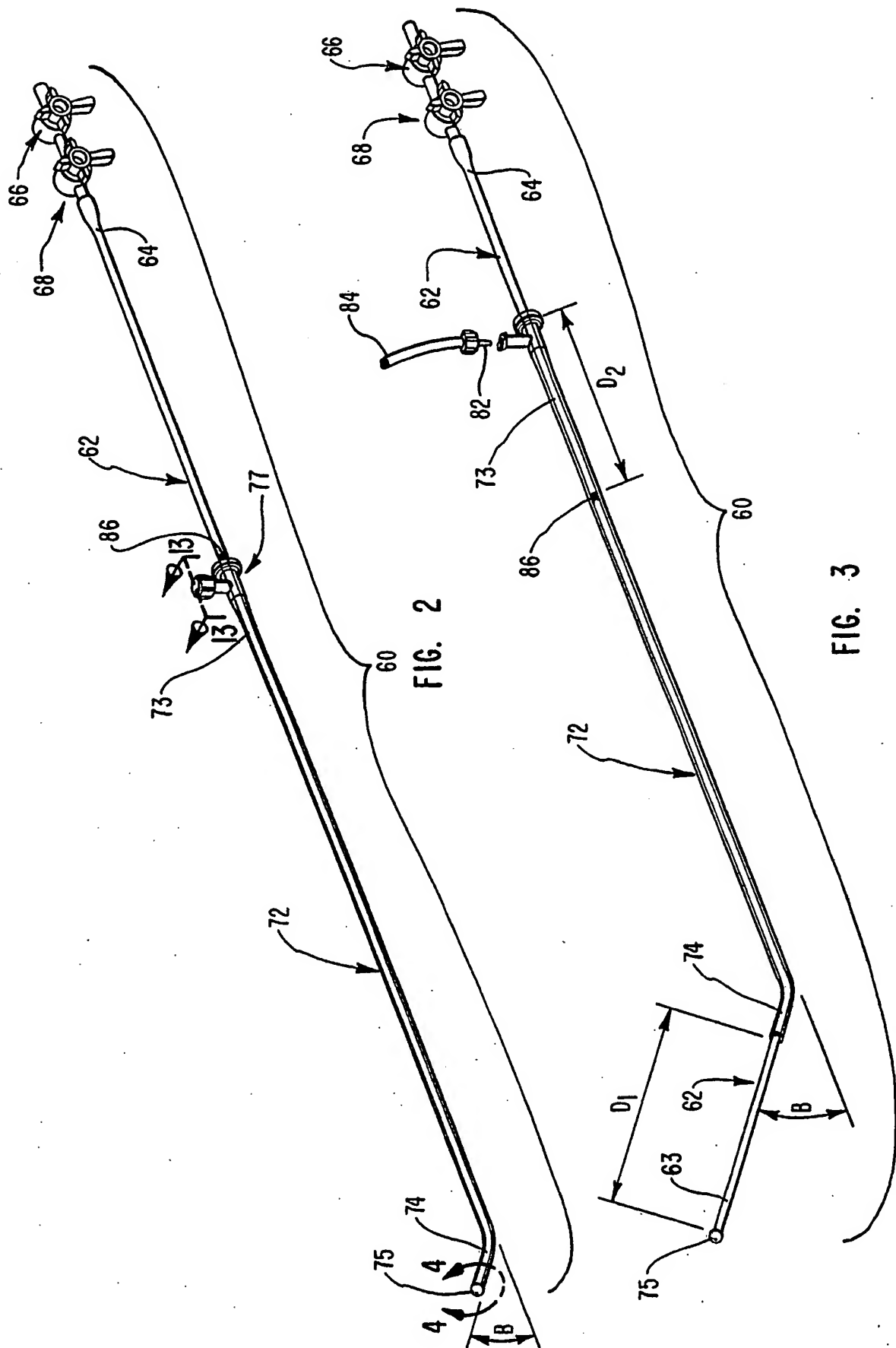


FIG. 2

FIG. 3

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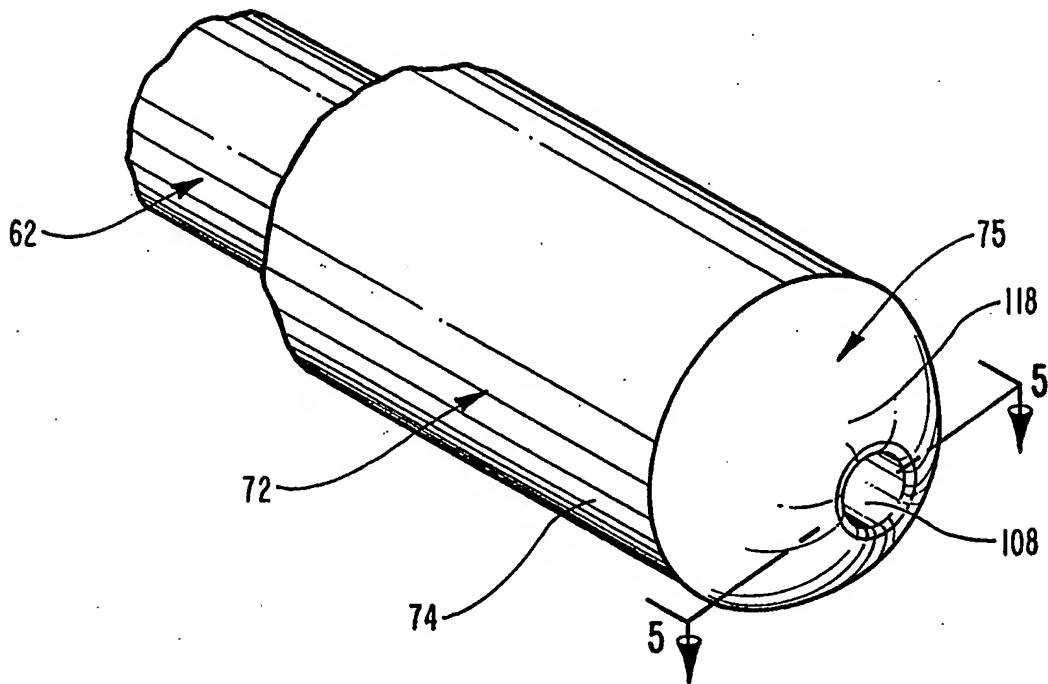


FIG. 4

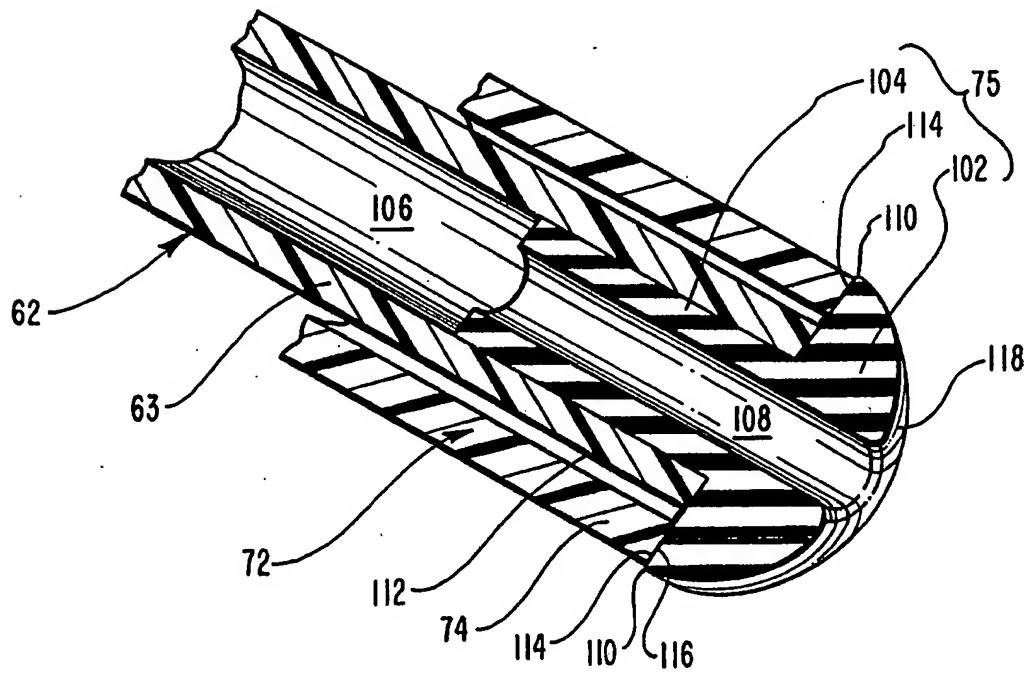


FIG. 5

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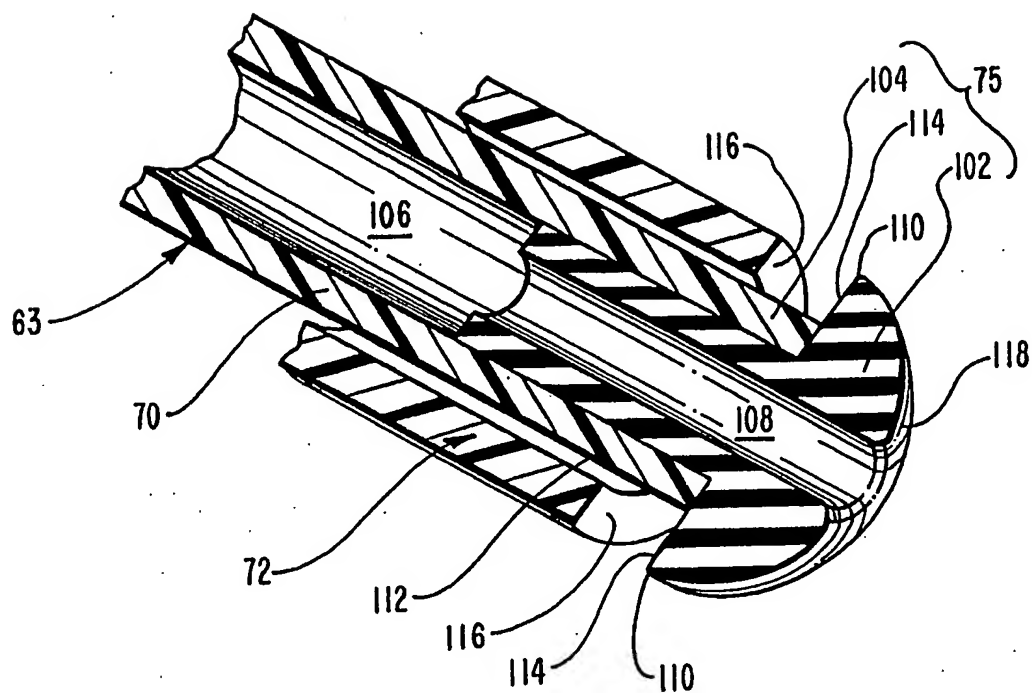


FIG. 6

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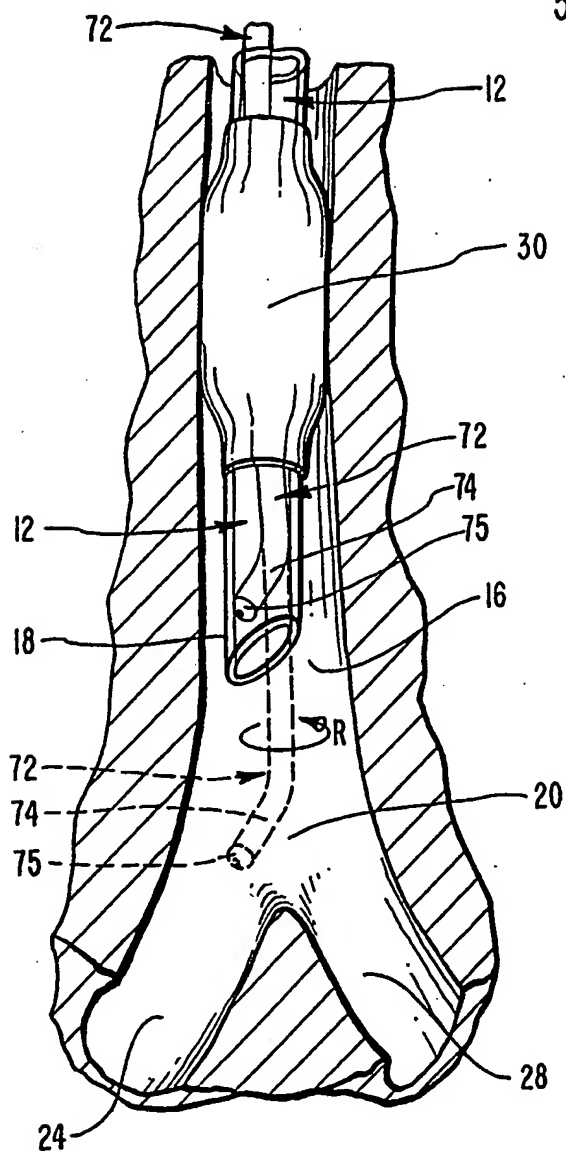


FIG. 7A

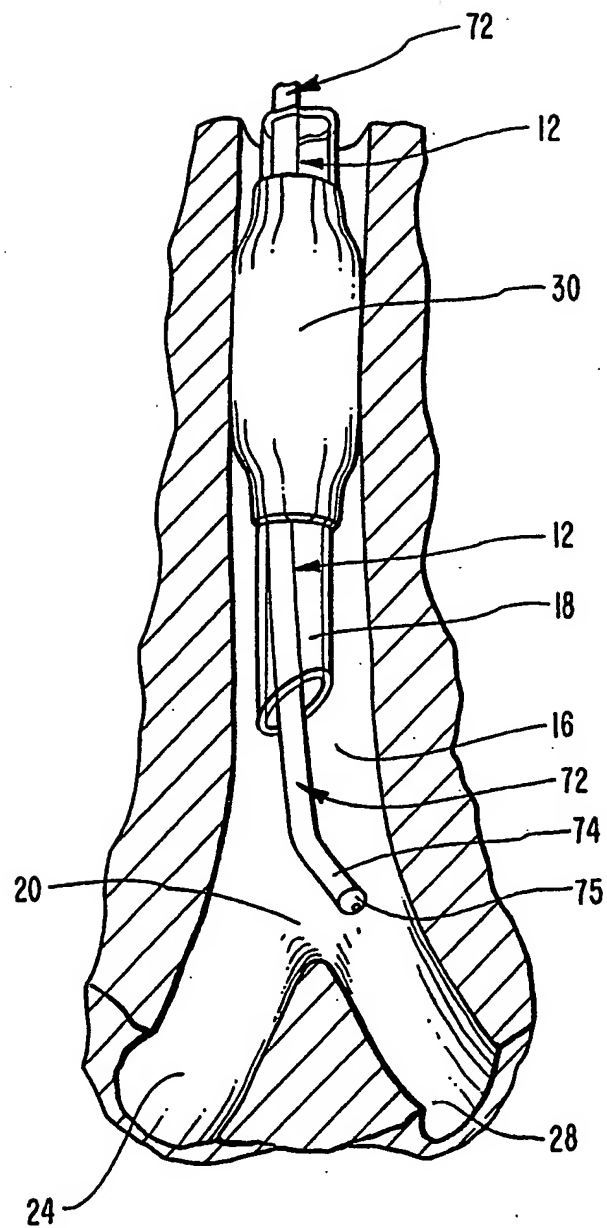


FIG. 7B

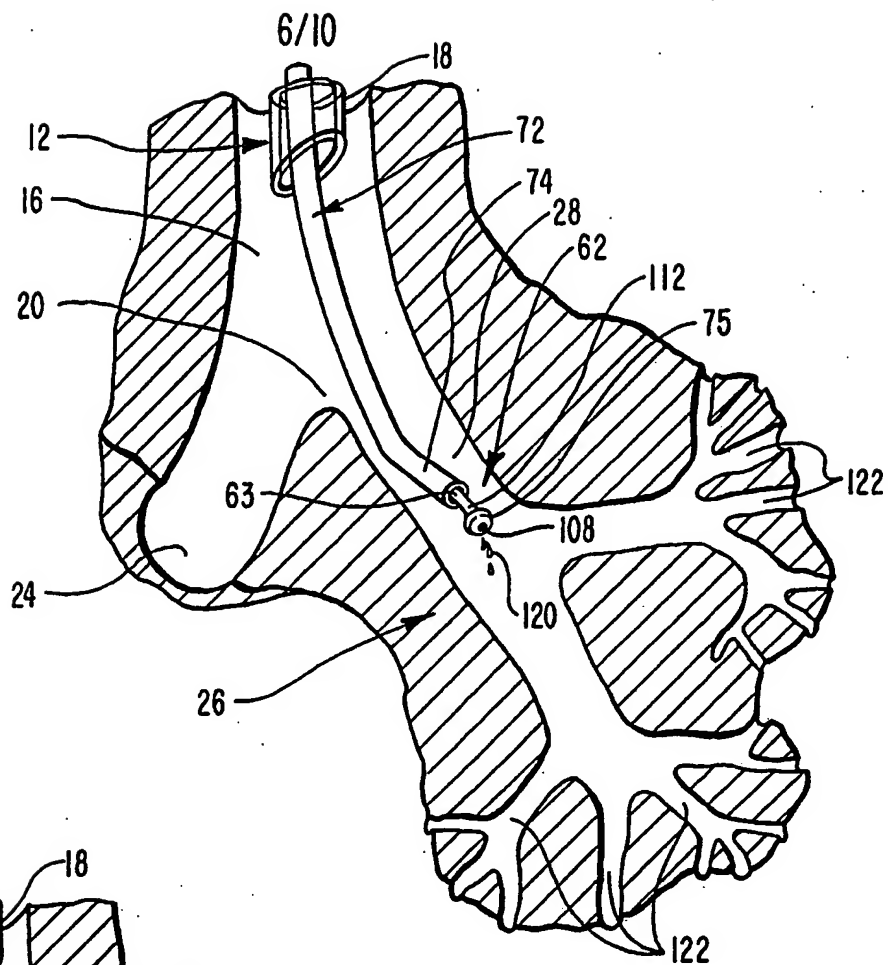


FIG. 7C

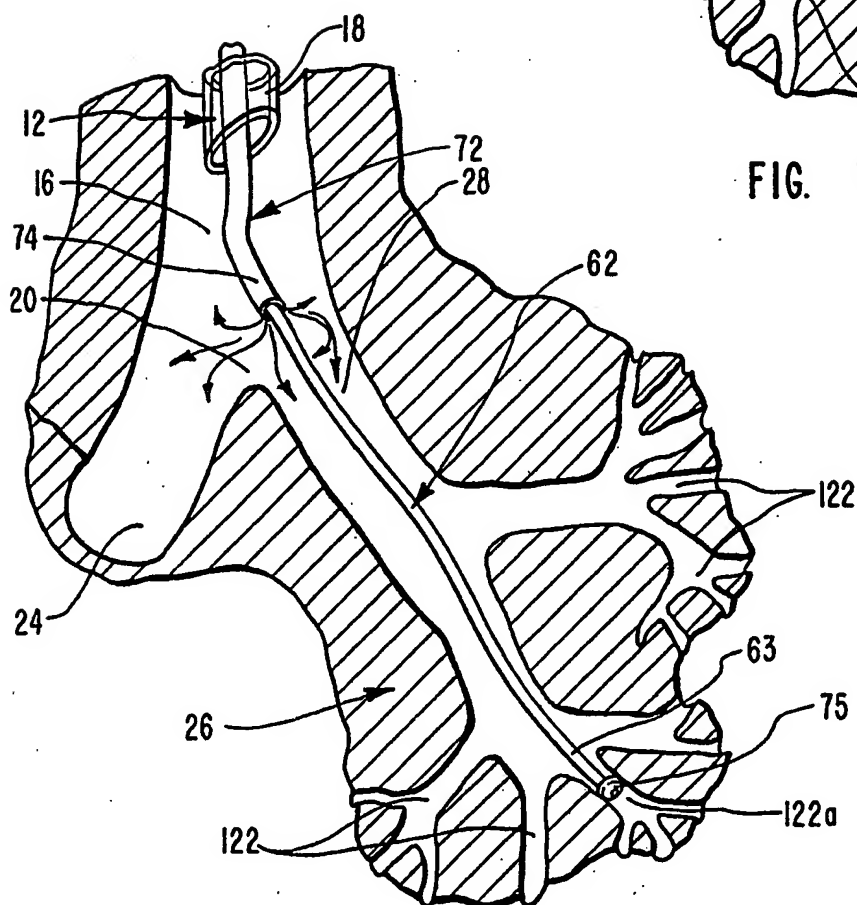


FIG. 7D

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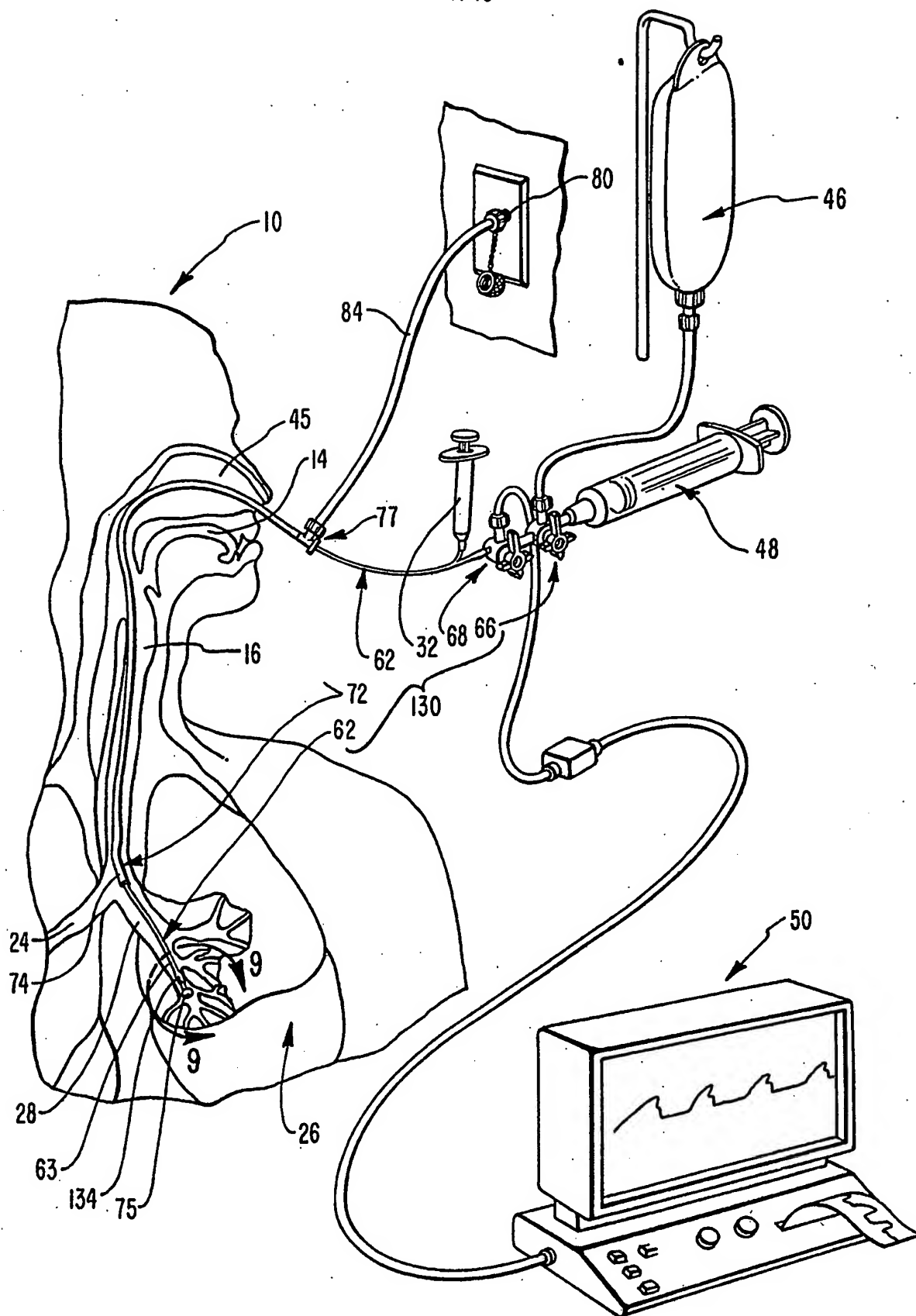
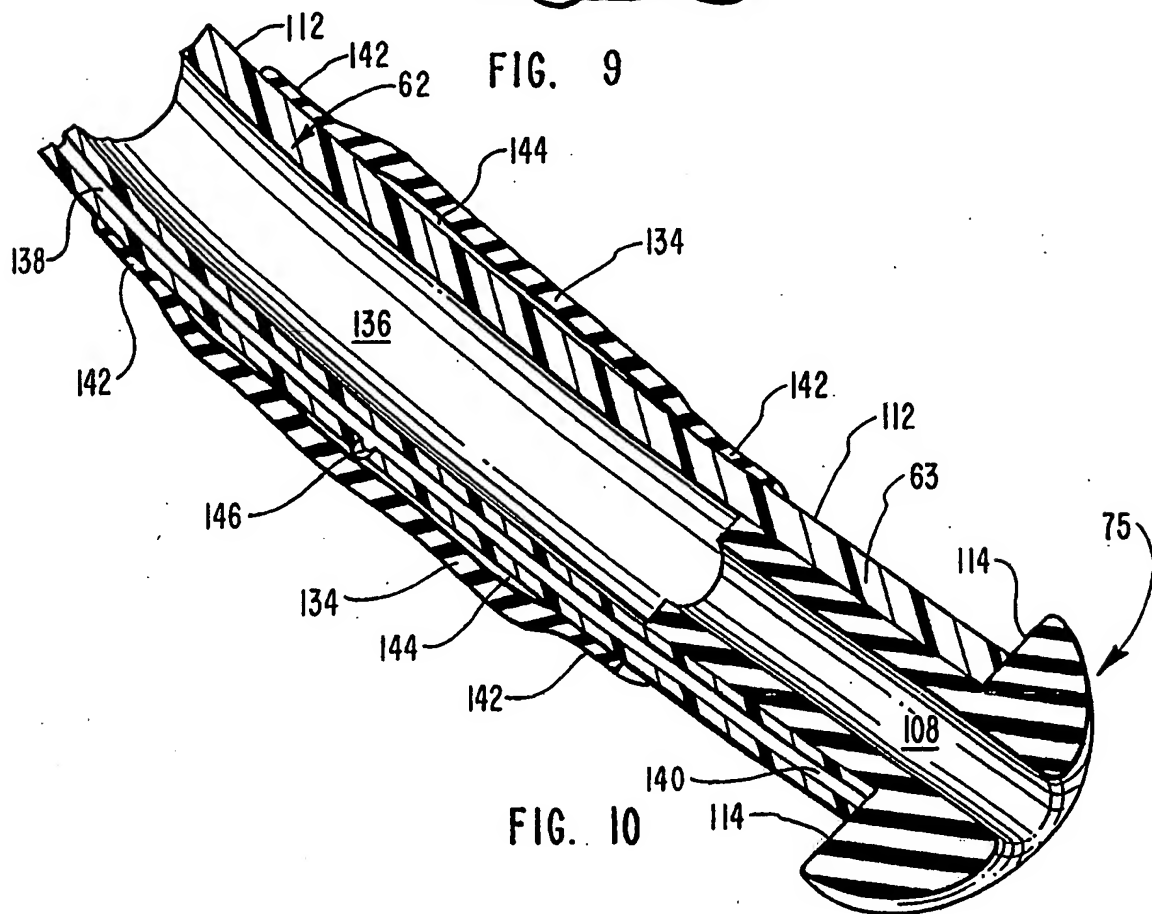
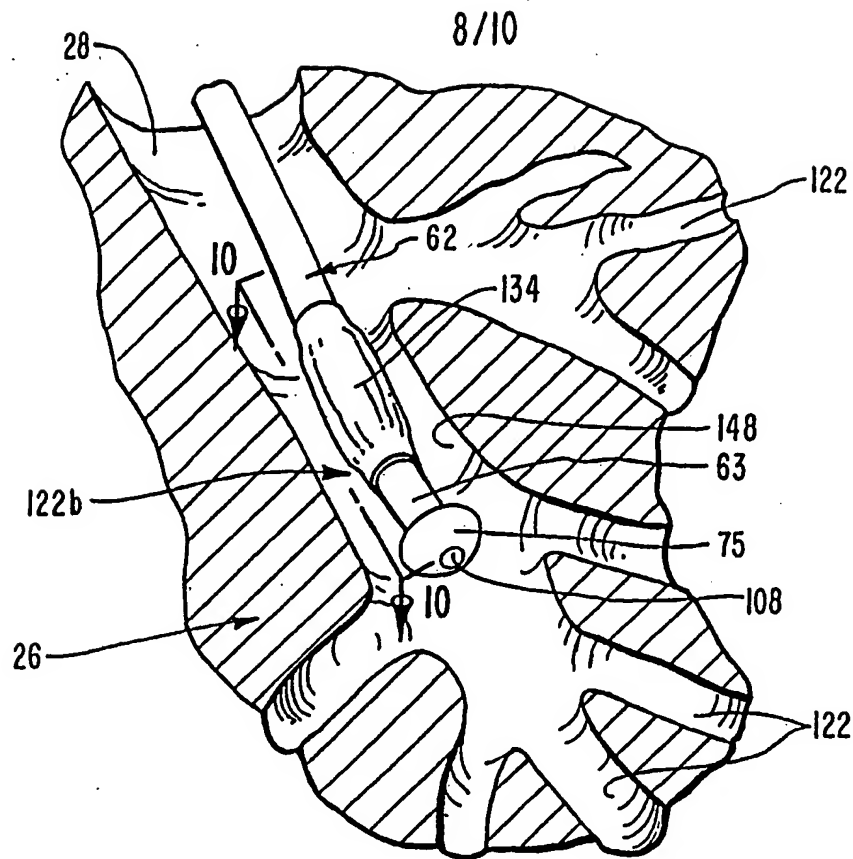


FIG. 8



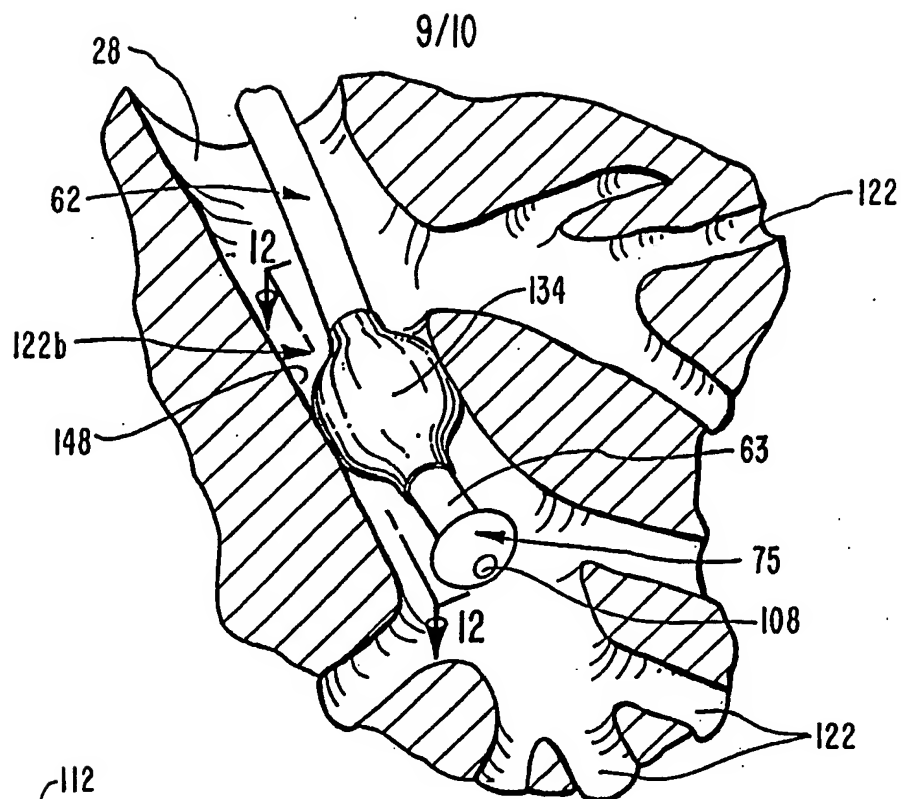
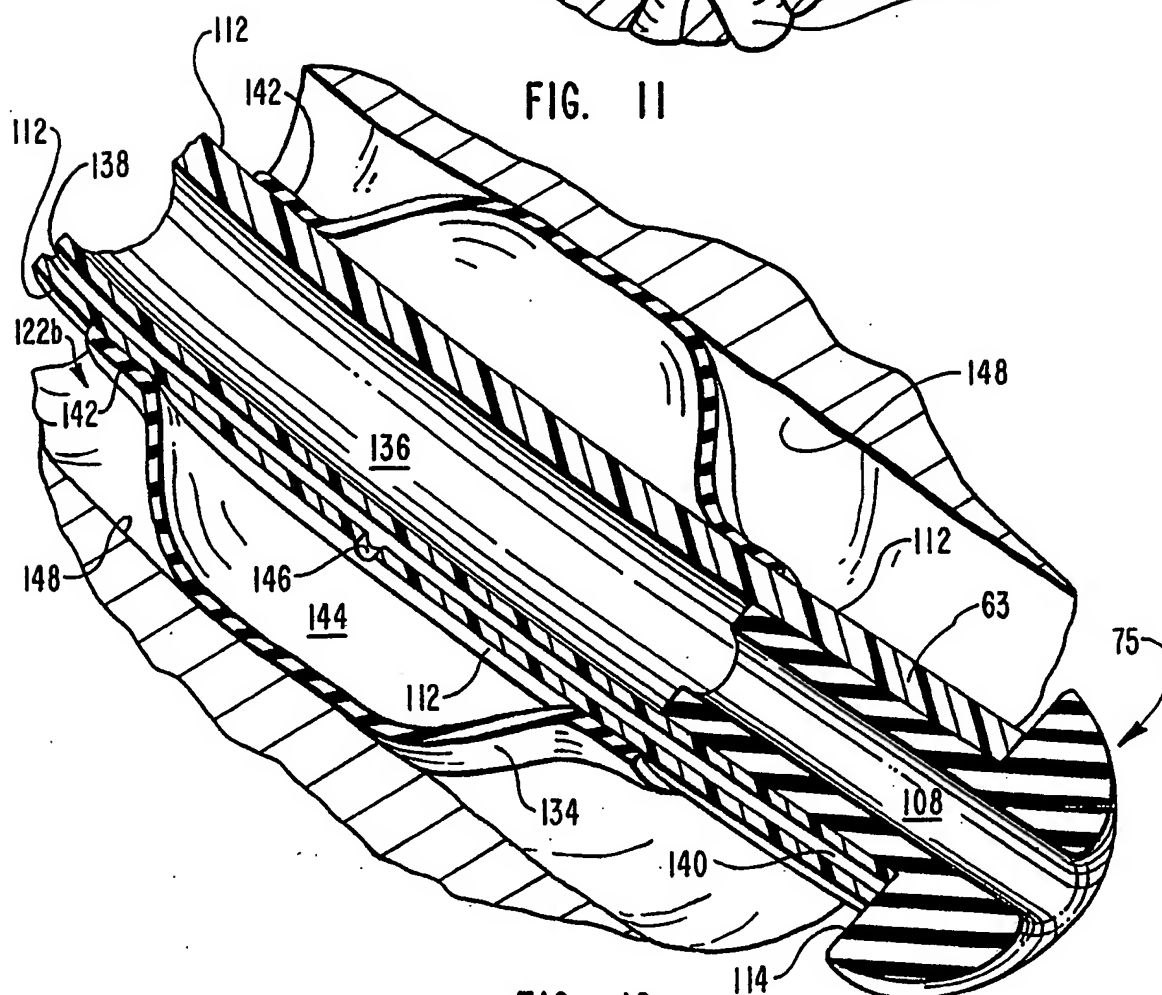


FIG. 11



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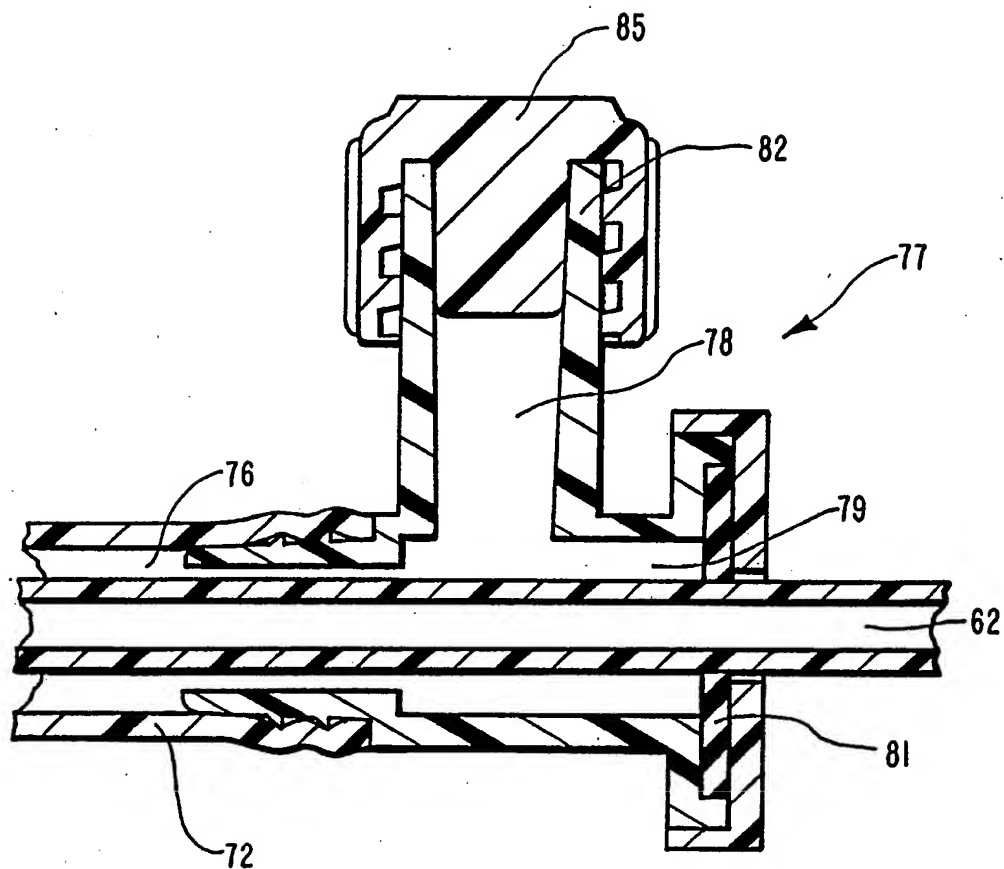


FIG. 13

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09732

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): A61B 5/00 U.S.CL. 128/768																										
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 5px;">Minimum Documentation Searched †</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; text-align: left; padding: 5px;">Classification System</th> <th style="text-align: left; padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px; vertical-align: top;">U.S.</td> <td style="padding: 5px;">128/749 10 604/19 36 54 158 187 280 606/106 750 11 27 38 93 167 236-283 760 28 48 95 171 239 284 768 35 49 96 181 264 902</td> </tr> </table> <div style="text-align: center; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ‡</div>			Classification System	Classification Symbols	U.S.	128/749 10 604/19 36 54 158 187 280 606/106 750 11 27 38 93 167 236-283 760 28 48 95 171 239 284 768 35 49 96 181 264 902																				
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III. DOCUMENTS CONSIDERED TO BE RELEVANT * <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; text-align: left; padding: 5px;">Category *</th> <th style="text-align: left; padding: 5px;">Citation of Document, † with indication, where appropriate, of the relevant passages ‡</th> <th style="text-align: left; padding: 5px;">Relevant to Claim No. ‡</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">US,A, 3,788,305 (SCHREIBER) 29 January 1974 (See entire reference)</td> <td style="padding: 5px;">1-3,19 47</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 3,788,305 (SCHREIBER) 29 January 1974 (See entire reference)</td> <td style="padding: 5px;">6,50,56-58</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 4,344,436 (KUBOTA) 17 August 1982 (See figure 2)</td> <td style="padding: 5px;">4,5,48,49 56-58,61</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 3,319,622 (SHINER) 16 May 1967 (See figures 1 and 2)</td> <td style="padding: 5px;">7-15, 20-36 44-46,56-58 61</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 4,072,146 (HOWES) 07 February 1978 (See element 43)</td> <td style="padding: 5px;">17,18,37, 51-55,56-59 61</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 4,819,664 (NAZARI) 11 April 1989 (See figure 4)</td> <td style="padding: 5px;">16,38-43 60</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A, 4,351,328 (BODAI) 28 September 1982 (See Figures 1-10)</td> <td style="padding: 5px;">62,63</td> </tr> </tbody> </table>			Category *	Citation of Document, † with indication, where appropriate, of the relevant passages ‡	Relevant to Claim No. ‡	X	US,A, 3,788,305 (SCHREIBER) 29 January 1974 (See entire reference)	1-3,19 47	Y	US,A, 3,788,305 (SCHREIBER) 29 January 1974 (See entire reference)	6,50,56-58	Y	US,A, 4,344,436 (KUBOTA) 17 August 1982 (See figure 2)	4,5,48,49 56-58,61	Y	US,A, 3,319,622 (SHINER) 16 May 1967 (See figures 1 and 2)	7-15, 20-36 44-46,56-58 61	Y	US,A, 4,072,146 (HOWES) 07 February 1978 (See element 43)	17,18,37, 51-55,56-59 61	Y	US,A, 4,819,664 (NAZARI) 11 April 1989 (See figure 4)	16,38-43 60	Y	US,A, 4,351,328 (BODAI) 28 September 1982 (See Figures 1-10)	62,63
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: †</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>																										
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search 05 May 1992 </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">22 MAY 1992</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority ISA/US </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> MAX HINDENBURG </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 05 May 1992	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">22 MAY 1992</div>	International Searching Authority ISA/US	Signature of Authorized Officer <div style="text-align: center;"> MAX HINDENBURG </div>																				
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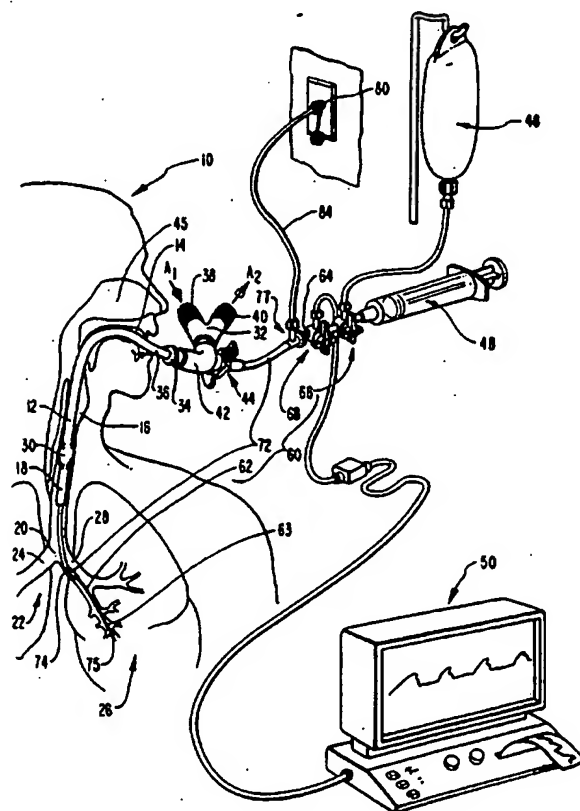
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(72) Inventor: STRICKLAND, Richard, D. ; 8890 South Sheffield Way, Sandy, UT 84093 (US).		Date of publication of the amended claims and statement: 20 August 1992 (20.08.92)	
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(54) Title: **BRONCHOALVEOLAR LAVAGE CATHETER**

(57) Abstract

An outer catheter (72) so sized and configured so as to extend from a point below the first bifurcation of the trachea through the upper respiratory system of the patient is disposed about an inner catheter (62) having a tip (75) secured in the opening at the distal end (74) thereof with an outer lateral periphery larger in diameter than the outer surface of the inner catheter. A passageway (76) is formed between said outer catheter (72) and said inner catheter (62). A connector hub assembly (77), connected to the proximal end (73) of the outer catheter (72) and couplable to a supply of oxygen, allows for oxygen insufflation to take place during the bronchoalveolar lavage procedure. The proximal surface of the tip (75) between the outer lateral periphery and the outer surface of the inner catheter (62) is capable of sealingly engaging the distal end (74) of the outer catheter (72). In this condition the pair of catheters can be advanced through the upper respiratory system of the patient without contaminating the outer surface of the inner catheter (62). Thereafter the inner catheter (62) is advanced relative to the outer catheter (72) into a wedging position in a bronchiole of the patient. In one embodiment, the inner catheter is provided with a selectively inflatable cuff by which to engage the walls of a bronchiole of the patient.



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AMENDED CLAIMS

[received by the International Bureau on 16 July 1992 (16.07.92);
original claims 1-63 replaced by amended claims 1-63 (17 pages)]

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1. An assembly for performing bronchoalveolar lavage, said assembly comprising:

5 (a) a sampling catheter so sized and configured as to extend from a bronchiole in the lung of a patient through the upper respiratory system of the patient, said sample catheter comprising proximal and distal ends and further comprising a single lumen means for both infusing and aspirating fluid therethrough, said single lumen means communicating with both said sampling catheter proximal and distal ends;

10 (b) means located at the proximal end of said sampling catheter for infusing and aspirating fluid through said single lumen means at said distal end; and

15 (c) means for directing the distal end of said sampling catheter into a preselected lung of the patient and for protecting the outside of said sampling catheter from contamination during advancement of said distal end of said sampling catheter through the upper respiratory system of the patient.

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2. An assembly as recited in Claim 1, wherein said means for directing and for protecting comprises an elongated insertion sheath having a proximal end and a distal end so sized and configured as to encircle said sampling catheter and to be capable of extending from below the first bifurcation of the trachea of the patient through the upper respiratory system of the patient.

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3. An assembly as recited in Claim 2, wherein said insertion sheath possess sufficient structural rigidity as to be capable, when disposed in the upper respiratory system of the patient, of exhibiting at the distal end

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1 thereof one-to-one rotation about the longitudinal axis
thereof relative to the proximal end thereof.

5 4. An assembly as recited in Claim 3, wherein the
distal end of said insertion sheath is displaced at a
predetermined bend angle to the longitudinal axis of said
insertion sheath.

10 5. An assembly as recited in Claim 4, wherein the
proximal end of said insertion sheath is provided with a
direction indicator designating the radial direction at
which said distal end of said insertion sheath departs from
the longitudinal axis thereof.

15 6. An assembly as recited in Claim 3, wherein said
insertion sheath is comprised of ethyl vinyl acetate.

20 7. An assembly as recited in Claim 2, wherein said
sampling catheter comprises a tip at the distal end
thereof, the outer lateral periphery of said tip having a
diameter larger than the outer surface of said sampling
catheter, said tip having a proximal surface between said
25 outer lateral periphery and said outer surface of said
sampling catheter capable of sealingly engaging said distal
end of said insertion sheath when said insertion sheath is
disposed encircling said sampling catheter with said distal
end of said sampling catheter at said distal end of said
insertion sheath.

30 8. An assembly as recited in Claim 7, wherein said
sampling catheter is provided with a position indicator
mark at the location on said sampling catheter disposed at
said proximal end of said insertion sheath when said tip of
said sampling catheter sealingly engages said distal end of
35 said insertion sheath.

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9. An assembly as recited in Claim 7, wherein the surface of said tip opposite from said proximal surface thereof defines a lead surface of said tip, and wherein said lead surface of said tip comprises a smoothly curving dome terminating at said outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said sampling catheter into a bronchiole of the patient.

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10. An assembly as recited in Claim 2, wherein said sampling catheter comprises a tip at the distal end thereof, said tip having a lead surface comprising a smoothly curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said sampling catheter into a bronchiole of a patient.

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11. An assembly as recited in Claim 10, wherein said tip has a diameter larger than the outer surface of said sampling catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface of said sampling catheter which sustains wedging of the distal end of said sampling catheter in a bronchiole of a patient.

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12. An assembly as recited in Claim 11, wherein said tip is comprised of a soft, biocompatible material, thereby to minimize trauma to patient tissue due to wedging of said distal end of said sampling catheter into a bronchiole of the patient.

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13. An assembly as recited in Claim 11, wherein said outer lateral periphery of said tip has a diameter larger than the diameter of the outer surface of said sampling catheter.

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14. An assembly as recited in Claim 13, wherein the
surface between said outer lateral periphery of said tip
and said outer surface of said sampling catheter defines a
proximal surface of said tip, and said proximal surface of
5 said tip is capable of sealingly engaging said distal end
of said insertion sheath when said insertion sheath is
disposed encircling said sampling catheter with said distal
end of said sampling catheter at said distal end of said
10 insertion sheath.

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15. An assembly as recited in Claim 14, wherein said
sampling catheter is provided with a position indicator
mark at the location on said sampling catheter disposed at
said proximal end of said insertion sheath when said tip of
said sampling catheter sealingly engages said distal end of
said insertion sheath.

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16. An assembly as recited in Claim 1, wherein said
sampling catheter comprises a flexible cuff attached to and
encircling the sides of said sampling catheter proximal of
said distal end thereof, said cuff being selectively
inflatable through said sampling catheter to engage the
walls of a bronchiole of the patient.

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17. An assembly as recited in Claim 1, wherein said
means for infusing and for aspirating comprises a sampling
stopcock located at said proximal end of said sampling
catheter, said sampling stopcock being connectable to a
30 reservoir of a fluid and to a syringe for infusing the
fluid through the sampling catheter.

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18. An assembly as recited in Claim 17, wherein said
sampling stopcock is capable of selectively placing the
syringe alternately in communication with the reservoir of
fluid or with said proximal end of said sampling catheter.

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19. A catheter for performing bronchoalveolar lavage, said catheter comprising:

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(a) an outer catheter so sized and configured as to extend from below the first bifurcation of the trachea of a patient through the upper respiratory system of the patient;

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(b) an inner catheter disposable inside said outer catheter and being so sized and configured as to extend from a bronchiole in the lung of a patient through the upper respiratory system of the patient, said inner catheter comprising proximal and distal ends and further comprising a single lumen means for both infusing and aspirating fluid therethrough, said single lumen means communicating with both said inner catheter proximal and distal ends; and

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(c) means located at said proximal end of said inner catheter for infusing and aspirating fluid through said single lumen means at said distal end.

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20. A catheter as recited in Claim 19, wherein said inner catheter comprises a first closure means located at said distal end of said inner catheter for sealing the distal end of said outer catheter when said outer catheter is disposed encircling said inner catheter with said distal end of said inner catheter at said distal end of said outer catheter.

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21. A catheter as recited in Claim 20, wherein said first closure means comprises a tip at the distal end of said inner catheter, said tip having an outer lateral periphery larger in diameter than the outer surface of said inner catheter, and said tip having a proximal surface between said outer lateral periphery and said outer surface of said inner catheter capable of sealingly engaging said distal end of said outer catheter when said outer catheter

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1 is disposed encircling said inner catheter with said distal
end of said inner catheter at said distal end of said outer
catheter.

5 22. A catheter as recited in Claim 21, wherein said
tip is secured in the opening at said distal end of said
inner catheter.

10 23. A catheter as recited in Claim 19, wherein said
inner catheter comprises a second closure means for
facilitating wedging of said distal end of said inner
catheter into a bronchiole of a patient.

15 24. A catheter as recited in Claim 23, wherein said
second closure means comprises a tip at said distal end of
said inner catheter, the lead surface of said tip
comprising a smoothly curving dome terminating at the outer
lateral periphery of said tip, said dome having formed
20 centrally therethrough an aperture communicating with the
interior of said inner catheter.

25 25. A catheter as recited in Claim 24, wherein said
tip is secured in the opening at said distal end of said
inner catheter.

30 26. A catheter as recited in Claim 19, wherein said
inner catheter comprises a tip at the distal end thereof,
the outer lateral periphery of said tip having a diameter
larger than the outer surface of said inner catheter, said
tip having a proximal surface between said outer lateral
periphery and said outer surface of said inner catheter
capable of sealingly engaging said distal end of said outer
catheter when said outer catheter is disposed encircling
said inner catheter with said distal end of said inner
35 catheter at said distal end of said outer catheter.

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27. A catheter as recited in Claim 26, wherein said inner catheter is provided with a position indicator mark at the location on said inner catheter disposed at said proximal end of said outer catheter when said tip of said inner catheter sealingly engages said distal end of said outer catheter.

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28. A catheter as recited in Claim 26, wherein the surface of said tip opposite from said proximal surface thereof defines a lead surface of said tip, and wherein said lead surface of said tip comprises a smoothly curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said inner catheter into a bronchiole of said patient.

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29. A catheter as recited in Claim 28, wherein said tip has a diameter larger than the outer surface of said inner catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface of said inner catheter which sustains wedging of the distal end of said inner catheter in a bronchiole of a patient.

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30. A catheter as recited in Claim 19, wherein said inner catheter comprises a tip at the distal end thereof, said tip having a lead surface comprising a smoothly curving dome terminating at the outer lateral periphery of said tip, thereby to facilitate wedging of said distal end of said inner catheter into a bronchiole of a patient.

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31. A catheter as recited in Claim 30, wherein said tip has a diameter larger than the outer surface of said inner catheter, whereby said tip has a proximal surface between said outer lateral periphery and said outer surface

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1 of said inner catheter which sustains wedging of the distal
end of said inner catheter in a bronchiole of a patient.

5 32. A catheter as recited in Claim 19, wherein said
inner catheter comprises a tip secured in the opening at
the distal end thereof, said tip having a mushroom-shaped
transverse cross-section.

10 33. A catheter as recited in Claim 32, wherein the
surface between said outer lateral periphery of said tip
and said outer surface of said inner catheter defines a
proximal surface of said tip, and said proximal surface of
15 said tip is capable of sealingly engaging said distal end
of said outer catheter when said outer catheter is disposed
encircling said inner catheter with said distal end of said
inner catheter at said distal end of said outer catheter.

20 34. A catheter as recited in Claim 33, wherein said
inner catheter is provided with a position indicator mark
at the location on said inner catheter disposed at said
proximal end of said outer catheter when said tip of said
inner catheter sealingly engages said distal end of said
outer catheter.

25 35. A catheter as recited in Claim 30, wherein said
tip is comprised of a radio-opaque material.

30 36. A catheter as recited in Claim 19, wherein said
inner catheter comprises a single lumen so sized as to
permit the infusion and aspiration of a fluid therethrough.

35 37. A catheter as recited in Claim 19, wherein said
inner catheter comprises:

1 (a) a first lumen so sized as to permit the
infusion and aspiration of a fluid through said inner
catheter; and

5 (b) a second lumen having a size relatively
smaller than that of said first lumen and being
capable of transmitting a gas between said distal and
said proximal ends of said inner catheter.

10 38. A catheter as recited in Claim 37, wherein said
inner catheter comprises a flexible cuff attached to and
encircling the sides of said inner catheter proximal of
said distal end thereof, said cuff being selectively
15 inflatable by a gas passed through said second lumen of
said inner catheter, thereby to engage the walls of a
bronchiole of the patient.

39. A catheter as recited in Claim 38, wherein said
inner catheter is a ten French catheter.

20 40. A catheter as recited in Claim 39, wherein said
outer catheter is a sixteen French catheter.

25 41. A catheter as recited in Claim 39, wherein said
outer catheter comprises an eighteen French catheter.

42. A catheter as recited in Claim 41, wherein said
inner catheter comprises a twelve French catheter.

30 43. A catheter as recited in Claim 19, wherein said
inner catheter comprises a flexible cuff attached to and
encircling the sides of said inner catheter proximal of
said distal end thereof, said cuff being selectively
inflatable to engage the walls of a bronchiole of the
35 patient.

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44. A catheter as recited in Claim 19, wherein said inner catheter is comprised of polyvinylchloride.

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45. A catheter as recited in Claim 19, wherein said inner catheter comprises a twelve French catheter.

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46. A catheter as recited in Claim 44, wherein said outer catheter is a sixteen French catheter.

47. A catheter as recited in Claim 19, wherein said outer catheter possess sufficient structural rigidity as to be capable, when disposed in the upper respiratory system of the patient, of exhibiting at the distal end thereof one-to-one rotation about the longitudinal axis thereof relative to the proximal end thereof.

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48. A catheter as recited in Claim 47, wherein the distal end of said outer catheter is displaced at a predetermined bend angle to the longitudinal axis of said outer catheter.

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49. A catheter as recited in Claim 48, wherein the proximal end of said outer catheter is provided with a direction indicator designating the direction at which said bend at said distal end of said outer catheter departs from the longitudinal axis thereof.

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50. A catheter as recited in Claim 47, wherein said outer catheter is comprised of ethyl vinyl acetate.

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51. A catheter as recited in Claim 19, wherein said means for infusing and for aspirating comprises a sampling stopcock located at said proximal end of said sampling catheter, said sampling stopcock being connectable to a

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1 reservoir of a fluid and to a syringe for infusing the
fluid through the inner catheter.

5 52. A catheter as recited in Claim 51, wherein said
sampling stopcock is capable of selectively placing the
syringe alternately in communication with the reservoir of
fluid or with said proximal end of said outer catheter.

10 53. A catheter as recited in Claim 19, further
comprising means for monitoring pressure in the airways of
the patient.

15 54. A catheter as recited in Claim 53, wherein said
means for monitoring pressure comprises a pressure stopcock
located between said proximal end of said inner catheter
and said means for infusing and aspirating.

20 55. A catheter as recited in Claim 54, wherein said
pressure stopcock is capable of selectively placing said
proximal end of said inner catheter in communication
alternatively with a pressure monitor or with said means
for infusing and aspirating.

25 56. A catheter for performing nonbronchoscopic
bronchoalveolar lavage, said catheter comprising:

30 (a) an elongated insertion sheath so sized and
configured as to extend from below the first
bifurcation of the trachea of the patient through the
upper respiratory system of the patient, said
insertion sheath possessing sufficient rigidity as to
be capable, when disposed in the upper respiratory
system of a patient, of exhibiting at the distal end
thereof one-to-one rotation about the longitudinal
axis thereof relative to the proximal end thereof,
said distal end of said insertion sheath being

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1 displaced at a predetermined bend angle to the longitudinal axis thereof;

5 (b) a sampling catheter disposable inside said outer catheter and being so sized and configured as to extend from a bronchiole of the lung of a patient through the upper respiratory system of the patient, said sampling catheter comprising proximal and distal ends and further comprising at least a single lumen for both infusing and aspirating fluids therethrough in communication with both said sampling catheter proximal and distal ends;

10 (c) a closure tip secured in said distal end of said sampling catheter, said closure tip comprising:

15 (i) an outer lateral periphery larger in diameter than the diameter of the outer surface of said sampling catheter;

20 (ii) a proximal surface between said outer lateral periphery thereof and said outer surface of said sampling catheter capable of sealingly engaging said distal end of said insertion sheath when said insertion sheath is disposed encircling said sampling catheter with said distal end of said sampling catheter at said distal end of said insertion sheath;

25 (iii) a lead surface at the opposite end of said closure tip from said proximal surface comprising a smoothly curving dome terminating at said outer lateral periphery of said closure tip, thereby facilitating wedging of said distal end of said sampling catheter into a bronchiole of the patient; and

30 (iv) an aperture centrally formed through said closure tip from said dome to the interior of said sampling catheter; and

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(d) a sampling stopcock located at the proximal end of said sampling catheter and connectable to a reservoir of a fluid and to a syringe for infusing the fluid through the sampling stopcock being capable of selectively placing the syringe alternately in communication with the reservoir of fluid or said proximal end of said sampling catheter, said communication being through said sampling catheter single lumen.

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57. A catheter as recited in Claim 56, further comprising a pressure stopcock located between said proximal end of said sampling catheter and said sampling stopcock, said stopcock being capable of selectively placing said proximal end of said sampling catheter in communication alternatively with a pressure monitor or with said sampling stopcock.

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58. A catheter as recited in Claim 56, wherein said sampling catheter comprises a single lumen so sized as to permit the infusion and aspiration of a fluid therethrough.

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59. A catheter as recited in Claim 56, wherein said sampling catheter comprises:

(a) a first lumen so sized as to permit the infusion and aspiration of a fluid through said sampling catheter; and

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(b) a second lumen having a size relatively smaller than that of said first lumen and being capable of transmitting a gas between said distal end said proximal ends of said sampling catheter.

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60. A catheter as recited in Claim 59, further comprising a flexible cuff attached to and encircling the sides of said sampling catheter proximal of said distal end

1 thereof, said cuff being inflatable by a gas passed through
said second lumen of said sampling catheter, thereby to
engage the walls of a bronchiole of the patient.

5 61. An assembly for performing bronchoalveolar
lavage, said assembly comprising:

10 (a) a sampling catheter having a proximal end
and a distal end, said sampling catheter so sized and
configured as to be capable of extending from a
bronchiole in the lung of a patient through the upper
respiratory system of the patient;

15 (b) means located at the proximal end of said
sampling catheter for infusing and aspirating fluid
through said sampling catheter;

20 (c) means for directing the distal end of said
sampling catheter into a lung of the patient and for
protecting the outside of said sampling catheter from
contamination during advancement of said distal end of
said sampling catheter through the upper respiratory
system of the patient; and

(d) means for allowing oxygen insufflation
during performance of bronchoalveolar lavage.

25 62. An assembly as recited in Claim 61, wherein said
means for allowing oxygen insufflation during performance
of bronchoalveolar lavage comprises a connector hub
assembly connected to said insertion sheath at said
proximal end of said insertion sheath, and in gaseous
communication with said passageway formed between said
30 sampling catheter and said insertion sheath, said connector
hub assembly comprising:

35 (a) an oxygen insufflation hub communicating at
one end thereof with the passageway formed between
said sampling catheter and said insertion sheath, and

1 couplable at the other end thereof with the supply of
oxygen; and

5 (b) a sealing hub communicating at one end
thereof with the passageway formed between said
sampling catheter and said insertion sheath, and at
the other end thereof with a protection means for
sealing said connector hub assembly, said protection
10 means encircling said sampling catheter tightly where
said sampling catheter passes through said connector
hub assembly, said protection means forming a seal
around said proximal end of said insertion sheath such
that oxygen entering said passageway formed between
15 said sampling catheter and said insertion sheath from
said oxygen insufflation hub is prevented from
escaping in the direction of said sealing hub.

63. A catheter for performing nonbronchoscopic
bronchoalveolar lavage, said catheter comprising:

20 (a) an elongated insertion sheath having a
proximal end and a distal end, said elongated sheath
so sized and configured as to extend from below the
first bifurcation of the trachea of the patient
through the upper respiratory system of the patient,
25 said insertion sheath possessing sufficient rigidity
as to be capable, when disposed in the upper
respiratory system of a patient, of exhibiting at the
distal end thereof one-to-one rotation about the
longitudinal axis thereof relative to the proximal end
thereof, said distal end of said insertion sheath
30 being displaced at a predetermined bend angle to the
longitudinal axis thereof;

(b) a sampling catheter having a proximal end and
a distal end disposable inside said outer catheter in
such way that there is a passageway formed between
35 said sampling catheter and said outer catheter, and

1 being so sized and configured as to extend from a
bronchiole of the lung of a patient through the upper
respiratory system of the patient;

5 (c) a closure tip secured in said distal end of
said sampling catheter, said closure tip comprising:

(i) an outer lateral periphery larger in
diameter than the diameter of the outer surface
of said sampling catheter;

10 (ii) a proximal surface between said outer
lateral periphery thereof and said outer surface
of said sampling catheter capable of sealingly
engaging said distal end of said insertion sheath
when said insertion sheath is disposed encircling
15 said sampling catheter with said distal end of
said sampling catheter at said distal end of said
insertion sheath;

(iii) a lead surface at the opposite end of
said closure tip from said proximal surface
20 comprising a smoothly curving dome terminating at
said outer lateral periphery of said closure tip,
thereby facilitating wedging of said distal end
of said sampling catheter into a bronchiole of
the patient; and

25 (iv) an aperture centrally formed through
said closure tip from said dome to the interior
of said sampling catheter;

(d) a sampling stopcock located at the proximal
end of said sampling catheter and connectable to a
30 reservoir of a fluid and to a syringe for infusing the
fluid through the sampling catheter, said sampling
stopcock being capable of selectively placing the
syringe alternately in communication with the
reservoir of fluid or said proximal end of said
35 sampling catheter; and

1

(e) a connector hub assembly for allowing oxygen insufflation during performance of bronchoalveolar lavage, said connector hub assembly being connected to said outer catheter at said proximal end of said outer catheter and in gaseous communication with said passageway formed between said sampling catheter and said insertion sheath, said connector hub assembly comprising:

5

10

(i) an oxygen insufflation hub communicating at one end thereof with the passageway formed between said sampling catheter and said outer catheter and couplable at the other end thereof with the supply of oxygen; and

15

(ii) a sealing hub communicating at one end thereof with the passageway formed between said sampling catheter and said outer catheter and at the other end thereof with a protection means for sealing said connector hub assembly, said protection means encircling said sampling catheter tightly where said sampling catheter passes through said connector hub assembly, said protection means forming a seal around said proximal end of said outer catheter such that oxygen entering said passageway formed between said sampling catheter and said outer catheter from said oxygen insufflation hub is prevented from escaping in the direction of said sealing hub.

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STATEMENT UNDER ARTICLE 19

25 Please amend the claims in the above-identified application by cancelling sheets 30 - 47 of this application which contain the claims and abstract. Please substitute therefore, sheets 30 - 47, attached hereto, which contain the new claims to be entered in this application. The abstract is identical to the abstract as set forth in the invitation.

30 The claims submitted herewith place claims 1-60 of this application into conformity with the amendments entered into the corresponding U.S. parent application.

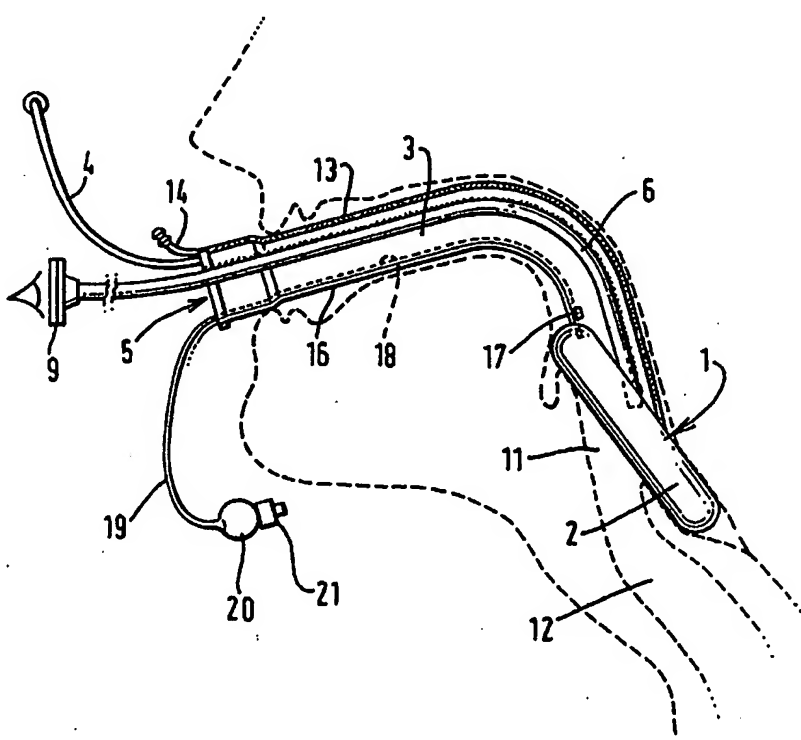
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61M 16/04, 16/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 95/33506 (43) International Publication Date: 14 December 1995 (14.12.95)</p>
<p>(21) International Application Number: PCT/GB95/01292 (22) International Filing Date: 5 June 1995 (05.06.95) (30) Priority Data: 9411215.8 4 June 1994 (04.06.94) GB (71)(72) Applicant and Inventor: BRAIN, Archibald, Ian, Jeremy [GB/GB]; Sandford House, Fran Court Gardens, Longcross Road, Longcross, Chertsey, Surrey KT16 0DJ (GB). (74) Agents: WEST, Alan, H. et al.; R G C Jenkins & Co., 26 Caxton Street, London SW1H 0RJ (GB).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published With international search report. With amended claims.</p>
<p>(54) Title: A FIBREOPTIC INTUBATING LARYNGEAL MASK AIRWAY</p> <p>(57) Abstract</p> <p>A laryngeal mask airway has an airway tube (3) substantially aligned with which there are provided one or two channels (6) containing fibreoptic bundles (7, 8) for emitting and receiving light which is directed into the mask aperture in order to provide a monoscopic or stereoscopic view of the laryngeal anatomy, to facilitate intubation of the trachea while maintaining ventilation of the lungs through the laryngeal mask, or to permit diagnosis or treatment of laryngeal or upper airway pathology.</p> 		

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A FIBREOPTIC INTUBATING LARYNGEAL MASK AIRWAY

This invention relates to a fiberoptic intubating laryngeal mask airway device for use in anaesthesia.

Laryngeal mask airway devices are described in
5 British Patents 2,111,394 and 2,205,499 and in a
number of corresponding foreign patents and patent
applications.

Despite the success of such laryngeal mask airway
(LMA) devices which are now used in some 40% of all
10 anaesthetic procedures in the United Kingdom,
intubation of the trachea remains the ultimate
objective of airway management in an emergency or when
there may be a risk of inhalation of gastric contents,
since the presence of a cuffed tube in the trachea
15 prevents gastric acid present in vomit from entering
and damaging the lungs. However, intubation of the
trachea is not always possible and, when difficulty is
experienced, soiling of the lungs with gastric acid
may occur while attempts are being made to intubate.
20 The LMA as described in the above patents has been
modified as described in British Patent 2,252,502 in
order to facilitate intubation of the trachea using
the LMA as a guide, in cases where intubation by
conventional means using a laryngoscope to visualise
25 the glottis has failed. However, this intubating
laryngeal mask (ILM) has the limitation that, for a

high degree of success in passing an endotracheal tube through the ILM tube into the trachea, fibrescopic aid is needed to ensure the endotracheal tube does not pass into the oesophagus or collide with the epiglottis. These hazards, particularly the former which may result in death if undetected, are present also in classical intubation using a laryngoscope. Fibreoptic assisted intubation is another possible technique when classical intubation fails but has the disadvantage that it requires much skill and takes time, a significant drawback in a situation where brain damage or death from lack of oxygen are never more than four minutes away if ventilation cannot be achieved. However, the LMA and the ILM have the advantages that if intubation turns out to be impossible, then the patient can still be kept alive because, unlike the laryngoscope or the fibrescope, the mask part of the LMA or ILM provides an adequate seal around the glottis to permit gentle positive pressure ventilation to be maintained while intubation attempts are taking place. This is an important advantage because in practice death or brain damage occur more often from failure to ventilate the lungs than from lung contamination with gastric contents.

In fibreoptic assisted intubation, the operator has to reach the laryngeal aperture by passing the

fibrescope around the back of the tongue (or through the nasal cavity and nasopharynx) and then passing the tip of the scope downwards until the larynx comes into view. This takes time, as previously stated, and because the scope is of small cross-section relative to the cross-section of the pharynx, it is possible for the tip of the fibrescope to wander to one side or the other of the pharynx on the way down, missing the structures of the laryngeal orifice. In addition, the tip of the scope is not protected from contamination with secretions present in the pharynx or from bleeding provoked by its passage, either or both of which may obscure the operator's view. Another problem is that the view is two-dimensional and the field of vision very restricted. The combination of all these factors makes fibreoptic assisted intubation a difficult skill to acquire and maintain. Lastly, fibreoptic scopes are very expensive and not all hospitals are able to afford or maintain them, which adds to the difficulty of ensuring skill is acquired by physicians who might need to use the technique.

These problems are partly resolved when the LMA or ILM is used as a guide for the fibrescope, since when correctly inserted, the mask part of the LMA or ILM completely fills the space of the lower pharynx when the cuff surrounding the mask is inflated. Time

to first ventilation is very rapid as the device is passed blindly in a single movement. Thus, when using the LMA, a view of the laryngeal inlet is automatically achieved in the great majority of cases simply by inserting the fibrescope down the tube. In other words, the tube-mask assembly acts as a guide, directing the fibrescope to its target. Furthermore, the inspection can be carried out in a leisurely fashion, since ventilation has already been assured as soon as the LMA cuff is inflated. With the ILM, the probability of viewing the larynx is even greater because unlike the LMA its tube is rigid and provided with an external handle, which permits direct manipulation of the mask relative to the larynx, allowing the clinician to alter the position of the mask if perfect alignment is not achieved in the first instance. However, a fibrescope still has to be inserted in the tube to ascertain whether accurate alignment has been achieved.

The present invention seeks to avoid this problem by incorporating into a modified laryngeal mast airway device one or more fibreoptic systems arranged to provide an optimal and preferably binocular view of the laryngeal inlet. This permits the operator to have immediate optical confirmation of the position of the mask aperture relative to the laryngeal inlet from

the moment of insertion of the device and at any time thereafter. A binocular view has the advantage of permitting stereoscopic vision of the anatomy.

In accordance with the present invention, there
5 is now provided a laryngeal mask airway device to facilitate lung ventilation in an unconscious patient, comprising an airway tube and a mask attached to an end of the airway tube, the mask having an annular peripheral formation of roughly elliptical shape and
10 being capable of conforming to and readily fitting within the actual and potential space behind the larynx so as to enable the annular peripheral formation to form a seal around the circumference of the laryngeal inlet without the device penetrating
15 into the interior of the larynx, the annular peripheral formation surrounding the mask into which the airway tube opens, the airway tube being curved to follow the airway of the patient, the device further comprising in alignment with the airway tube at least
20 one channel adapted to contain a fibreoptic system for receiving and emitting light directed into the mask.

Several advantages accrue from achieving immediate optical confirmation of the position of the mask, as follows.

25 (a) If regurgitant fluid finds its way into the bowl of the mask before intubation of the trachea can

be carried out, then it can immediately be seen and aspirated using a suction catheter before significant lung contamination occurs.

5 (b) Visual information from the fibrescope can be transferred to a television screen for remote viewing, for example as part of the monitoring equipment on the anaesthetic machine.

10 (c) As with other monitoring aids, this information can be stored for future use in teaching or as part of the patient's case notes, for example for medico-legal evidence.

(d) The laryngeal view can also be valuable as a teaching aid during routine anaesthesia.

15 (e) Laryngeal movements indicating inadequate levels of anaesthesia can be seen, permitting early preventive action to avoid the danger of laryngeal spasm or awareness.

20 (f) The device may be used for diagnosis and treatment of laryngeal or tracheal pathology, for example by ear, nose and throat specialists.

(g) Like the standard LMA, the device can be inserted in the awake patient after application of local anaesthesia to the throat, offering the possibility of treatment and diagnosis of upper airway problems on an outpatient basis.

(h) Most importantly, in the case that

intubation of the trachea with an endotracheal tube is desired; the laryngeal view from the mask aperture will help the clinician to guide the tip of the tube towards the laryngeal aperture by manipulating the handle of the rigid laryngeal mask tube through which the endotracheal tube is passed.

Two forms of laryngeal mask airway device in accordance with the invention will now be described by way of example only with reference to the accompanying drawings, in which:

Figures 1 and 2 are side and front views, respectively, of a first form of the device; and

Figure 3 is a side view of a second form of the device.

Referring first to Figures 1 and 2 of the drawings, the first form of laryngeal mask airway device of the invention comprises a mask body 1 attached to a rigid curved airway tube 3 and surrounded by a generally elliptical peripheral formation, or cuff, 2. The body 1 and cuff 2 are of generally conventional construction and configuration and are described in detail in the patents referred to above. The airway tube 3 is of substantially rigid construction and may be made of plastics material, carbon fibre, metal or any combination of these materials and has an exterior handle 4 and

incorporates a main airway lumen 5, and one or two additional channels 6 running on one or both sides and substantially parallel to the plane of curvature of lumen 5. The channel(s) 6 accommodate fibreoptic bundles 7 incorporating fibres connected to a light source (not shown) which may be remote from the airway device or incorporated for example in its handle 4. Running alongside the fibreoptic bundles 7 are separate fibre bundles 8 whose functions is to transmit the image of the object so illuminated to the observer's eyes, those separate fibre bundles 8 being sheathed in visible-light impermeable material and running from independently focusable eyepiece or eyepieces 9 situated so as to avoid encumbering intubation attempts. Both fibre bundles 7 and 8 terminate within or close to the airway opening 10 of the mask at such an angle as to offer a view of the larynx and in the case of two separate channels 6 each such channel is suitably directed with respect to the other so as to provide a stereoscopic view of the larynx 11 to the observer viewing through eyepieces 9. Additionally, the combined light-source carrying and viewing fibreoptic bundles 7 and 8 may be moveable within channels 6 so as to permit an observer to obtain varying views of anatomical structures in the region of the larynx. Additionally, again, fibreoptic

bundles 7 and 8 may be of sufficient length to permit their entry into the trachea 12 or bronchi should examination of these structures be desired. In the preferred case where there are provided two separate
5 fibreoptic channels 6, fibreoptic bundles 7 and 8 are preferably independently moveable in their respective channels so that it is possible to view simultaneously two different anatomical regions, permitting for example the effect of stimulation or treatment on one
10 region to be seen on another region remote from the region of such treatment or stimulation.

In addition to the main airway tube 3 and channel or channels 6, there is provided optionally a further channel 13 which runs substantially parallel to airway
15 tube 3 and may be disposed at any point in the circumference on the wall of airway tube 3 but is preferably sited in the midline of the convex surface of curvature of airway tube 3. This additional channel 13 opens at the outer or mouth end of the
20 device into a tube 14 suitable for attachment to plastics disposable suction catheters (not shown) and opening at the laryngeal end into the mask where it forms a drain 15 for collection of secretions from the lungs, pharynx or stomach, blood, foreign bodies or
25 food particles. The drain 15, channel 13 and tube 14 are of sufficient diameter to permit passage of

suction catheters (for example, of 5-6 mm diameter in adults).

Optionally, there may further be provided in the wall of main airway tube 3 a small channel 16 (for example, of approximately 1 mm internal diameter) which connects externally of the patient to a tube of similar diameter leading to a device (not shown) known as a capnometer for measuring end-tidal carbon dioxide concentrations in exhaled breath. The channel 16 terminates at gas sampling site 17 within the interior lumen of main airway tube 3 near to its junction with mask 1.

Again optionally, there may be provided a further small channel 18 (for example, of approximately 0.5 mm internal diameter) running longitudinally in the wall of main airway tube 3, the external opening of that channel 18 connecting to a flexible tube 19 which in turn connects with a pilot balloon 20 and self-sealing valve 21 suitable for gas-tight insertion of a disposable syringe for inflation of the device with air. The internal end of that channel 18 communicates with the interior of the inflatable cuff 2 so that the cuff may be inflated or deflated via that channel 18.

Additionally it should be understood that airway tube 3 is provided with easily removable friction-fit (15 mm) connector (not shown) designed for attachment

to conventional anaesthetic gas hosing, in order that the device may be used alone to ventilate the lungs of a patient, without using the intubation facility. It should also be understood that to prevent loss of airway pressure, channels 6, 13 and 16 are provided with means (not shown) to prevent leakage of gas through them to the exterior when gas is delivered under pressure through main airway tube 3.

In the alternative form of laryngeal mask airway device shown in Fig. 3 of the accompanying drawings, the airway tube 3' is of softer and of more pliable construction and includes along its outer radius a channel 13' similar to the channel 13 in the device shown in Fig. 1 but of larger diameter, and which may be closed by a bung 22. In this construction, the rigid handle 4' extends into and along that channel 13' at least during insertion of the device into the patients, and after the device had been properly positioned the handle 4' may be removed. The channel 13' may then be used in the same manner as the channel 13 in the device shown in Fig. 1 for aspirating any unwanted fluids or secretions, as described above. Still further, the channel 13' may be of sufficiently large diameter to pass a removable fiberoptic scope, thereby obviating the need for the channels 6 and dedicated fiberoptic bundles 7 and 8 in the device

shown in Fig. 1. In this connection, the enlarged diameter channel 13' will of course present a correspondingly enlarged drain 15' close to the airway opening 10 of the mask and through which the fibreoptic scope will be able to obtain an acceptable image of the patient's larynx. As shown in Fig. 3, the other features of the device shown in Fig. 1 are retained and the same reference numerals have been used in Fig. 3 to identify them.

The novel features of the present invention may be incorporated into any form of laryngeal mask device and should not be considered to be restricted to incorporation in the forms of the device detailed above. For example, the gastro-laryngeal mask described in US Patent 5,241, 956 and containing a facility for drainage of oesophageal discharge in addition to an extra posteriorly placed cuff for greater sealing efficacy, may with advantage be adapted to include the features described herein, as may the laryngeal mask fitted with a reflectance type oximeter described in US Patent 5,282,464.

CLAIMS:

1. A laryngeal mask airway device to facilitate lung ventilation in an unconscious patient, comprising an airway tube (3,3') and a mask (1) attached to an end of the airway tube, the mask having an annular peripheral formation (2) of roughly elliptical shape and being capable of conforming to and readily fitting within the actual and potential space behind the larynx so as to enable the annular peripheral formation to form a seal around the circumference of the laryngeal inlet without the device penetrating into the interior of the larynx (11), the annular peripheral formation surrounding the mask into which the airway tube opens, the airway tube being curved to follow the airway of the patient, the device further comprising in alignment with the airway tube at least one channel (6,13') adapted to contain a fibroptic system (7,8) for receiving and emitting light directed into the mask.

2. A device according to claim 1, wherein two channels (6) are located along the sides of the airway tube (3).

3. A device according to claim 1 or claim 2, which includes also a further channel (13) aligned

with the airway tube (3) and opening into the mask (1) forming a drain for secretions from the lungs, pharynx or stomach.

4. A device according to claim 1, wherein the
5 channel (13') is located along the outer radius of the airway tube (3') and forms also a drain for secretions from the lungs, pharynx or stomach.

5. A device according to any one of claims 1 to
10 4, which includes also a still further channel (16) aligned with the airway tube (3) for connection to a capnometer.

AMENDED CLAIMS

[received by the International Bureau on 17 November 1995(17.11.95);
new claim 6 added; remaining claims unchanged (1 page)]

with the airway tube (3) and opening into the mask (1)
forming a drain for secretions from the lungs, pharynx
or stomach.

4. A device according to claim 1, wherein the
5 channel (13') is located along the outer radius of the
airway tube (3') and forms also a drain for secretions
from the lungs, pharynx or stomach.

5. A device according to any one of claims 1 to
4, which includes also a still further channel (16)
10 aligned with the airway tube (3) for connection to a
capnometer.

6. A device according to claim 1, wherein the
airway tube (3') is pliable and wherein the channel
(13') is located along the outer radius of the airway
15 tube and is adapted to receive a rigid handle (4').

1/2

FIG. 1

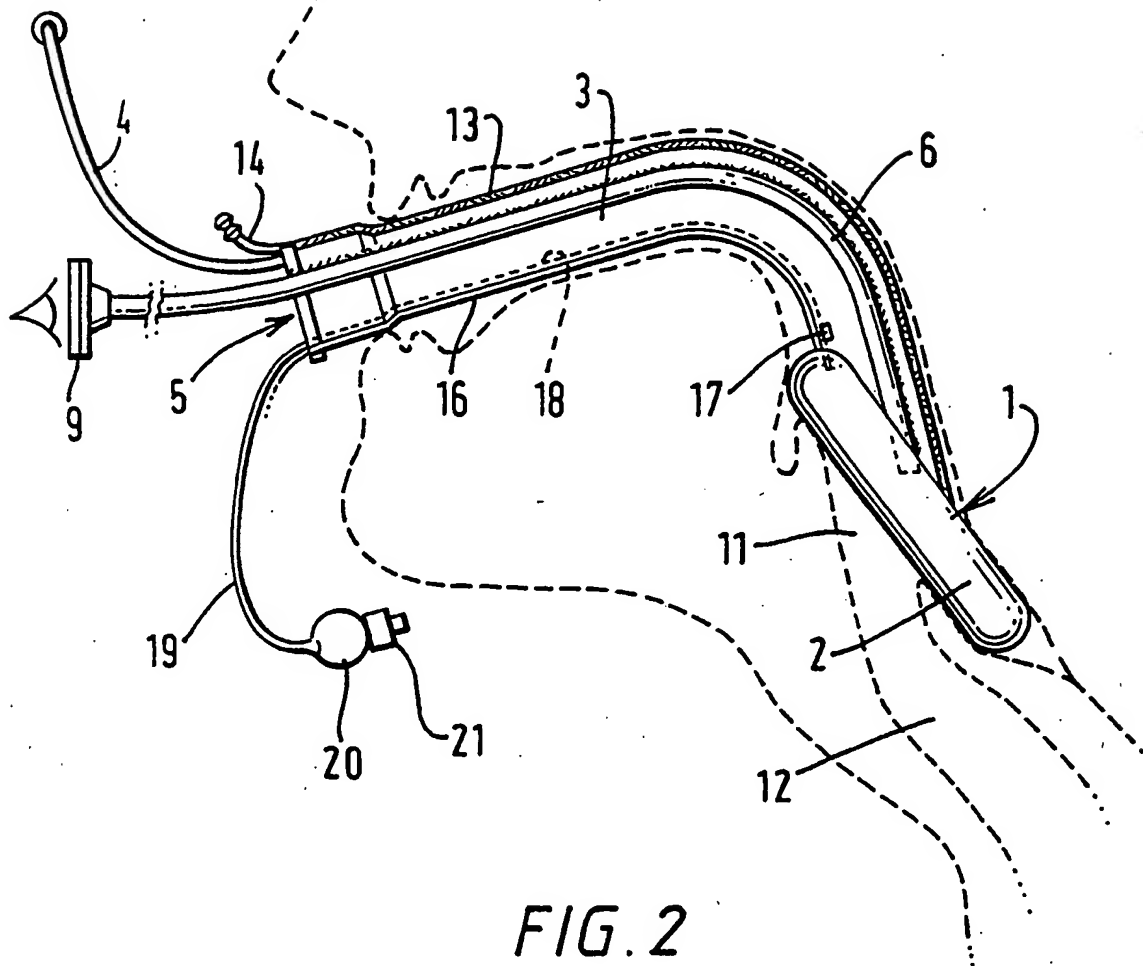
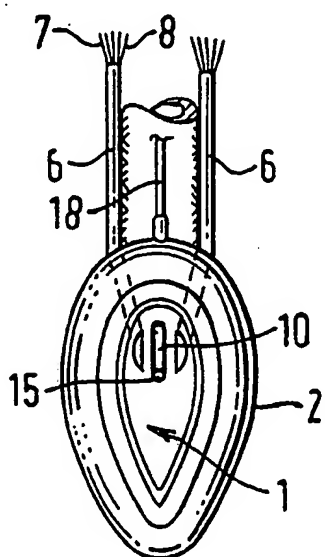
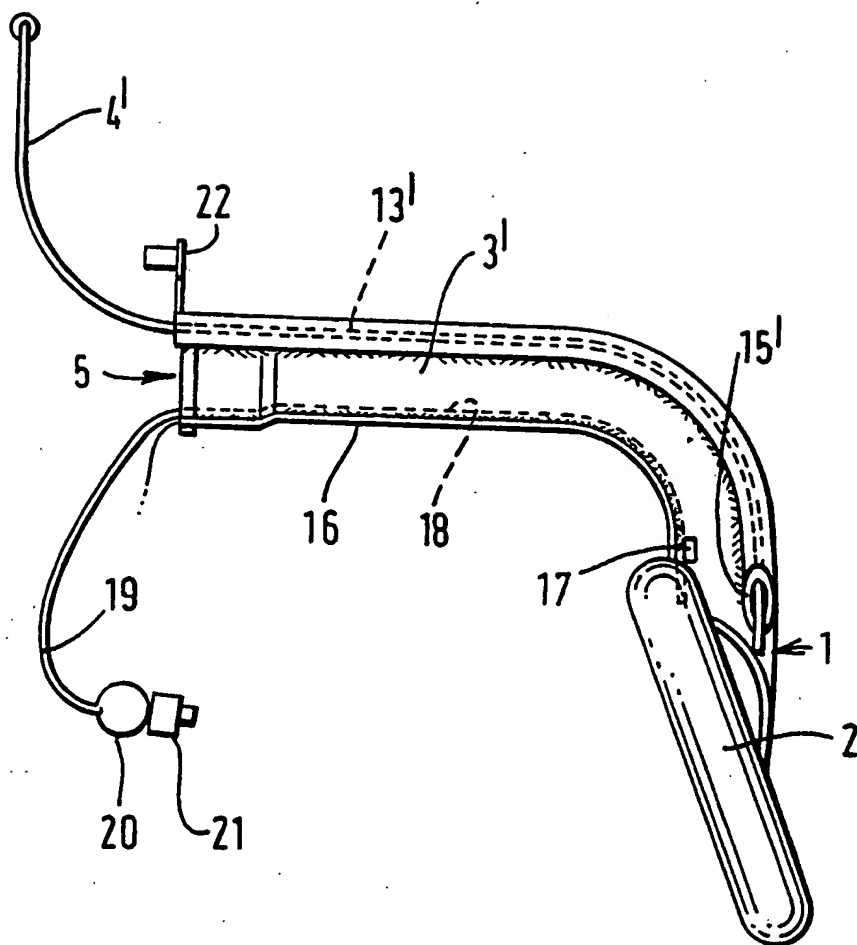


FIG. 2



2/2

FIG. 3



INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 95/01292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M16/04 A61M16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 13587 (BRAIN) 20 August 1992 cited in the application see claim 1; figures 1,2 ---	1,3,4
Y	WO,A,91 07201 (PARKER) 30 May 1991 see page 35, line 4 - line 19; figures 9-11 see page 39, line 8 - page 40, line 8 ---	1,3,4
A	US,A,5 285 778 (MACKIN) 15 February 1994 see column 2, line 55 - column 3, line 2; figure 3 ---	1,2
A	US,A,4 976 261 (GLUCK ET AL.) 11 December 1990 see column 5, line 7 - line 19 -----	5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

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		US-A- 5339805	23-08-94

US-A-5285778	15-02-94	NONE	

US-A-4976261	11-12-90	NONE	

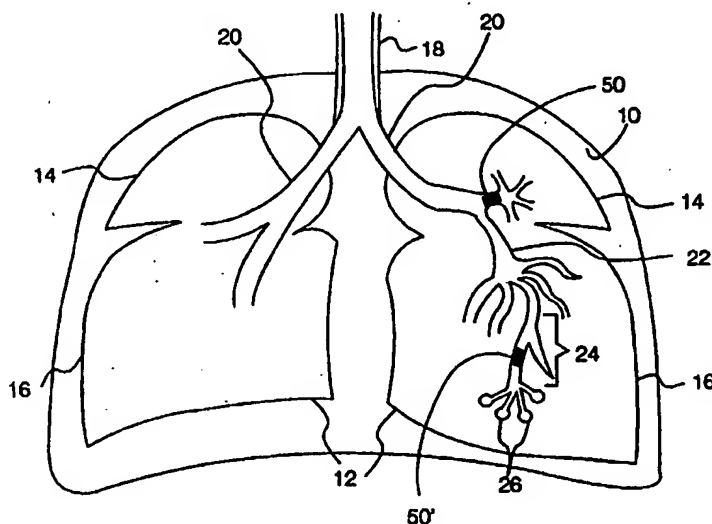


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(54) Title: OCCLUSION DEVICE



(57) Abstract

An obturator for a bronchial tube or tubule of a human or animal lung comprises a blocking element (92) and a securing element (90). The blocking element serves to seal the tube or tubule against the passage of fluid past the obturator when the obturator is disposed in a bronchial tube or tubule. The securing element serves to retain the blocking element in position. The blocking element comprises a substantially cylindrical plug of biocompatible, resiliently deformable closed-cell foamed plastics material, such as PVC. The securing element comprises a stent having barbs (98) to engage and retain the blocking element. The stent also has anchors (100) to retain the stent in a bronchial tube or tubule. A method of treatment of emphysema or other lung conditions or diseases in human or animal patients comprises placing an obturator in a bronchial tube or tubule of the patient so as to seal the tube or tubule against the passage of fluid past the obturator.

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OCCLUSION DEVICE

- 5 The present invention relates to a device useful in the treatment of emphysema and other diseases or disorders of the human or animal lung.

Emphysema is a disease of the lung caused primarily by prolonged smoking, although not exclusively thereby. It
10 is an unrelentless, intractable and debilitating process. Emphysema is defined as an abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis. In this context, destruction means non-
15 uniformity in the pattern of respiratory airspace enlargement; orderly appearance of the acinus is disturbed and may be lost.

Emphysema causes a physiological loss of lung elastic recoil, which decreases expiratory airflow by loss of
20 driving pressure and premature airway closure from reduced airway traction. The effect of this is that the alveoli become hyper-inflated without there being any real exchange of air with the outside. Therefore the patient begins to feel starved of oxygen and so attempts

to breathe more deeply. In breathing more deeply, the effects are exacerbated.

Not only are those individual alveoli which have a block in their respective bronchial tubules affected, but also
5 neighbouring alveoli, perhaps in other regions of the lung, which may otherwise be perfectly serviceable, become affected because the hyper-inflated alveoli pressurise neighbouring alveoli and prevent them from expanding fully. There is, of course, a relatively fixed
10 "exchange" volume of an individual's lung, that is to say, the difference between the expanded volume and the deflated volume. Emphysema reduces the exchange volume because undeflated alveoli occupy that space. Consequently, the only recourse available to the patient
15 is to increase the expanded volume, thereby resulting in the barrel chest symptomatic of emphysema sufferers.

The major therapeutic modalities currently available consist of bronchodilator and anti-inflammatory drugs, directed at decreasing airway resistance, and antibiotics
20 to treat acute and chronic infection. Supplemental oxygen therapy for the hypoxaemic patient improves exercise performance and improves survival in patients with cor pulmonale. Despite all available medical therapies, the course of the disease is one of

progressive limitation, increasing dyspnoea and significant increase in overall mortality.

It has long been realised that full lung volume is more than enough for survival in most circumstances and that
5 a person can survive quite satisfactorily with only one lung, for example. Heterogenous distribution of emphysema, together with the lack of pulmonary blood flow to those areas have made lung volume reduction surgery a logical option. Removal of parts of the lung affected by
10 emphysema permits unaffected areas to become operative again and so enable a better quality of life for the patient. Clearly, however, such invasive procedures are of a very serious nature and some patients will not, in any event, be in a sufficiently strong condition to
15 accept the trauma of such procedures. Primarily, the basic relief for emphysema sufferers is inactivity, on the one hand, and breathing pure oxygen, on the other.

Emphysema is a distressing condition affecting a relatively large proportion of the population, and a more
20 effective and less traumatic treatment is required.

On a different matter, other lung conditions sometimes lead to bleeding into the lung. A patient having this condition feels movement of the blood caused by airflow in the lung during breathing, and perceives the blood as

a foreign body and irritant. The patient coughs in an attempt to dislodge the perceived foreign body. Coughing blood, of course, is sometimes the first warning of a more serious disease or condition, but once that is realised, there is no benefit in such bleeding. Moreover, in such conditions where the lung might heal itself and subsequently stop bleeding, or indeed simply where the bleeding needs to be confined, the coughing reaction, which is almost impossible to resist, does not help the situation at all, and merely spreads the blood to other areas of the lung.

Therefore it is an object of the present invention to provide a method of treatment of certain lung conditions or diseases and to provide a device for such treatment.

15 In accordance with a first aspect of the present invention there is provided a method of treatment of emphysema or other lung conditions or diseases, the method comprising placing an obturator in a bronchial tube or tubule so as to seal the tube or tubule against the passage of fluid past the obturator.

In the case of emphysema, and by the simple expedient of inserting an obturator in a bronchial tube, a section of a lung can be isolated so that no air can be drawn into it. Thereafter, the isolated part deflates in time as the

air remaining in it becomes absorbed, and so that part of the lung stops affecting other areas of the lungs, which can thus perform normally. Such a procedure is relatively simple, requiring only a delivery device for the obturator, which device is inserted through the mouth and airway of the patient until the proposed placement site is reached, whereupon the device is activated to release the obturator from the device.

In the case of bleeding into the lung, an obturator stops the flow of blood. The lung is tamponated by the obturator and blood merely collects in the isolated part of the lung and ultimately, if the bleeding stops, will be reabsorbed. Alternatively, in the case of some, perhaps terminal, conditions such as some lung cancers, it at least provides temporary relief for the patient.

In accordance with a second aspect of the invention there is provided an obturator for a bronchial tube or tubule of a human or animal lung comprising a blocking element and a securing element.

Preferably the two elements are separate components, the blocking element serving to seal the tube or tubule against the passage of fluid past the obturator when the obturator is disposed in a bronchial tube or tubule, and

the securing element serving to retain the blocking element in position in the tube or tubule.

The blocking element preferably comprises a substantially cylindrical plug of biocompatible material. The plug may
5 comprise resiliently deformable closed-cell foamed plastics material, such as PVC, so that it may be compressed to facilitate insertion into the tube or tubule and thereafter expand to fill the cross-section of the tube or tubule.

10 It is known to employ stents in medical fields to expand and support collapsed blood vessels, and indeed bronchial tubes. A stent is a compressible framework which, when inserted into a vessel and released, expands and, within the limits of its expansion, supports and possibly
15 expands the walls of the vessel.

Preferably, the securing element comprises a stent. The stent may have barbs to engage and retain the blocking element. The stent preferably also has anchors to retain the stent in a bronchial tube or tubule.

20 In one embodiment, the stent comprises a crown of surgical quality steel wire legs in zig-zag formation. Said barbs and anchors may depend from points of the

crown. Preferably the crown is closed in its circumference, although this is not essential.

In another embodiment, the stent comprises a dome of surgical quality steel wire legs. Said barbs and anchors
5 may be formed on the ends of said legs.

It is known in medical fields to block blood vessels, for example where a genetic or other defect has resulted in a hole which needs blocking, or, for example, in the case of babies whose aortic to pulmonary artery connection has
10 not closed following birth, a condition known as patent ductus arteriosus. In the case of holes, it is well known to employ an "umbrella", where a diaphragm of material forms the seal against the blood vessel wall, the handle of the umbrella serving to keep the diaphragm
15 across the vessel. In the case of babies, it has also been known to employ a plug of PVC foam to treat patent ductus arteriosus, the plug encouraging clotting.

However, in the case of bronchial tubes and tubules a diaphragm seal is not been used yet, although its
20 application cannot be entirely ruled out. For example, an umbrella device with a larger surface area of contact with the bronchial mucosa might be as effective.

In blood vessels a complete seal is seldom required because any leak soon blocks by the formation of a clot; something that would not happen in an airway of a lung. Secondly, airways are not always absolutely circular in section, so a circular diaphragm may not always make a
5 good seal, at least around some parts of the circumference, unless it has capacity to expand in all radial directions and has a large contact area.

However, a complete seal is an absolute requirement of
10 the present invention (at least over the period of a single breath), because without it, air can leak past during inhalation and pressurise the lung in just the same way, and perhaps even to a greater extent. More importantly, however, a patient with such an obturator in
15 place can only feel its presence if there is movement of air around it to stimulate adjacent nerve endings. Once a patient can feel the obturator, there will be irresistible compulsion to cough which, if done excessively, may be sufficient to dislodge the obturator.

20 Thus it has been found that a very effective seal is achieved by the use of said cylindrical plug of foamed PVC (of the type commonly employed as earplugs). The effectiveness of this arrangement is probably due to the fact that any leakage path has to be a long one and there
25 are thus numerous opportunities for it to close and seal

about at least one closed circuit around the plug. Another reason is that a plug can mould itself to the shape of the tube or tubule, which is itself unlikely to be cylindrical, or, indeed, circular in cross-section.

- 5 Preferably, the method of the present invention employs an obturator of the type defined above.

The delivery device preferably comprises a delivery tube in which the obturator is received in a compressed state at a distal end thereof, a guide tube, which is capable
10 of following a possibly tortuous path under the guidance of a surgeon from entry into the mouth of a patient, down the patient's trachea and one bronchus to a proposed delivery site in a bronchial tube or tubule, and which has a passage to receive the delivery tube therealong,
15 and release means to eject the obturator from the delivery tube and guide tube.

The obturator needs to slide in the delivery tube during ejection and the stent provides a low friction surface of the obturator to facilitate such ejection.

- 20 It is feasible that the blocking and securing elements may be integrally formed from plastics material, and wherein the securing element comprises adhered or fused anchor elements on the blocking element.

It is also feasible that the securing element may comprise a memory metal which is released to its normal expanded shape by a physical parameter, for example, the passage of an electric current therethrough, once it has
5 been inserted at the proposed location. Otherwise it is in the same form as the above described steel stent which relies on resilience for its expansion. The advantage of a memory metal device is that it requires no compression during insertion so that the delivery tube of the
10 delivery device may be replaced by a simple guide rod to which it is connected.

The invention will be better understood from the following description of particular embodiments given as non-limiting examples. The description refers to the
15 accompanying drawings, in which :-

Figure 1 shows a section through the human chest indicating the location of bronchial obturators in the lungs;

Figure 2 shows a bronchial obturator complete with
20 delivery system;

Figures 3a b and c show in perspective two embodiments of an obturator according to the present invention, that of Figure 3a having a crown stent, and that of Figure 3b having a dome stent, Figure 3c being a

crown stent in an open configuration prior to rolling and, optionally, welding into a ring as in Figure 3a;

Figures 4a and b show an internal barb and external anchor respectively;

5 Figure 5 is a perspective view of another embodiment of obturator in accordance with the present invention; and,

10 Figure 6 is a perspective view of yet another embodiment of obturator also in accordance with the present invention.

In Figure 1 of the drawings, a human chest cavity 10 includes a pair of lungs 12 which each comprise upper and lower lobes 14,16. A trachea 18 branches into two bronchi 20, which further branch into bronchial tubes 22 and segmental bronchi 24. The bronchi 24, after further branching, terminate in alveoli 26.

In the majority of patients suffering from emphysema, it frequently effects mainly the upper lobes 14 of the lungs, leaving the lower lobes 16 unaffected, or at least less affected. However, if no treatment is given to a patient, the expansion effect of the upper lobes as the condition develops presses on the lower lobes and reduces their capacity to perform efficiently. Lower lobe emphysema does occur in some patients, and in which event
25 it is then the upper lobes which are compressed.

Thus the present invention suggests placing an obturator 50 in a bronchial tube or tubule to isolate the region of the lung supplied by that tube or tubule. Where the obturator is placed will be decided by the surgeon and
5 will depend on the how localised the damaged region of lung is. That is to say, if the whole lobe is badly affected, then the obturator is placed in the lobar bronchus 22 supplying that lobe (as shown at 50 in Figure 1). On the other hand, if the damage is more localised,
10 then the obturator will be placed in a smaller segmental bronchus 24, (as shown at 50' in Figure 1). Thus more than one obturator may be employed in the same pair of lungs isolating different regions of them. They will also be of different sizes, depending where they are to
15 be inserted.

The above considerations equally apply when the condition being treated is not emphysema but some other condition which a doctor considers can usefully be treated by the method of the present invention. Such another condition
20 is where a lung, or part of it is bleeding into the airway and an obturator isolates the bleeding region and inhibits coughing which may damage the lung further, or at least cause further discomfort to the patient.

Figure 2 shows an endo-bronchial obturator 50 complete
25 with delivery device 70. The delivery device comprises a

handle 72 and flexible guide tube 74. Slidably received
in the guide tube is a delivery tube 76 having the
obturator 50 disposed at its distal end 78. A release
means 80 is insertable in a proximal end 82 of the
5 delivery tube 82 and by means of which the obturator 50
may be ejected from the end of the delivery tube. The
guide tube is guided down the trachea and into the
appropriate bronchus by means of guide lines (not shown)
which enable the delivery system to be turned to follow
10 the desired course. Optical guidance means may be
included, or real-time X-ray or other monitoring methods
may be employed to guide the surgeon. Once the end of
the guide tube reaches the correct location, the delivery
tube is inserted in the handle end of the delivery device
15 70, and then the release means 80 is pushed down the tube
82 to eject the obturator. The obturator is adapted to
expand or be expanded, when ejected, to fill and block
the tube or tubule in which it is inserted.

As can be seen from Figure 3a, the obturator 50 in its
20 first embodiment is comprised of two main components, a
securing element in the form of a stent 90, and a
blocking element in the form of a closed-cell, PVC foam
plug 92.

The stent 90 is constructed from a plurality of legs 91
25 of surgical grade stainless steel wire welded together

such that when extended the stent appears as a series of connected 'W's, as shown in an unconnected disposition in Figure 3c. Indeed, it is not essential that the final connection between ends 94,96 be made to form a closed crown arrangement (as shown in Figure 3a); it is equally effective merely to roll the stent 90b as indicated by arrows in Figure 3c.

When the two ends of the stent are joined together, the stent 90 folds into a circular frame or crown, capable of encompassing the biocompatible block 92. The stent is constructed so as to be of a size slightly smaller (in its unstressed condition) than the block, so that its natural resilience squeezes the block slightly. On the other hand, the stent should be larger than the airway into which it is to be introduced so that it presses outwardly against the wall of the airway, and is incorporated into the mucosa of the air passage.

The legs 91 of the stent crown are fitted with both internal barbs 98 and external anchors 100. The barbs 98 embed themselves in the block 92 and secure the block to the stent 90. The anchors 100 are adapted to engage the walls of the patient's airways to hold the stent in position.

Figure 4a shows an internal barb 98. The internal barb, also constructed from surgical quality stainless steel, is substantially straight and has a hook 99 at one end. The hooked end 99 is the point and means by which the
5 barb is secured to the biocompatible block.

Figure 4b shows an external anchor 100. The anchor, which is also constructed from surgical quality stainless steel, is again substantially straight and has a coil 101
10 at its end. A coil is used so that damage is not caused to the tissue of the airway in which the obturator is fitted, particularly if and when the obturator is removed.

The barbs and anchors are joined to the stent crown by a
15 welded joint between two adjacent legs 91. Barbs can alternate with anchors at the same end of the stent, or one end can have all barbs, while the other end has all anchors. Both arrangements are shown in Figures 3a and c respectively.

20 A different embodiment of obturator 50b, also in accordance with the present invention, is shown in Figure 3b in which surgical quality stainless steel wires are all welded together at a point 104 to form a domed stent 90b. Legs 91b are alternately turned inwards to form
25 barbs 98b, or outwards to form anchors 100b.

Alternatively, all the legs could be anchors 100b, with interspersed shorter barbs 98bb, as one is shown in dashed lines in Figure 3b.

5 The aforementioned obturators all rely on resilience of the steel to return the stent to its original shape once released from the delivery mechanism and so as to enable fitment in a narrower tubule than the unstressed size of the stent would otherwise allow. However, this requires prestressing the stent and keeping it stressed during
10 delivery. Thus the present invention may find suitable application for memory metals, which only return to their original shape when some physical condition changes, for example, temperature rise or electrical current flow.

15 It is essential for the blocking device 50 to be comprised of a resiliently deformable material such as PVC foam as mentioned above. This enables the blocking device to be easily surrounded by the stent 90 and deformed into a compact structure, thereby enabling delivery of the block to its destination in the lung.

20 It is likewise essential that the block be capable of expanding and reforming into its original shape once deposited in the desired location in the lungs. It should be noted that the block is deformed and reformed in both an axial and a radial direction. It is the block 92

which seals a bronchial tube or tubule; mucous surrounds the block and forms a fluid tight seal. The presence of the stent around the block does not inhibit sealing in any way since the stent is essentially incorporated into the mucosa lining the airway.

Under compression, PVC foam has a high coefficient of friction which would prevent ejection from the delivery device as described above, if it was not surrounded by the stent 90, which offers a relatively low friction surface to the inside of delivery tube 76.

However, it is feasible that the block 92 could include a low friction surface to enable such ejection without the stent. Instead of the stent as described above, anchor means might be moulded in biocompatible plastics material as a crown, for example, on one end of the block, and either be adhered, fused or otherwise bound thereto.

The effectiveness of the device depends, to some extent, on the length of the block. Moreover, the block is required to be of a size which is both comfortable to the patient once expanded in the lung and which expands to completely obstruct the passage of air into the affected portions of the lung. The extended size of the block therefore ranges between 5mm and 25mm in length, and

between 5 and 11mm in diameter, depending on the size of the tube or tubule to be obturated.

Obturator 50c shown in Figure 5, comprises a balloon 200, which is inflated after insertion and then detached. The
5 balloon is captivated in an appropriate securing device such as stent 202. In this case, the barbs would not be sharp, but would merely retain ends of the balloon, or, as shown, would comprises turned-in points 204,206 at each end of the stent.

10 Finally, as mentioned above, the obturator may be as shown at 50d in Figure 6, where it comprises a diaphragm 300 expanded by an internal stent 302 having anchors 302. One end 306 of the diaphragm is attached to the stent to retain it on the stent. The diaphragm is also adhered to
15 the stent.

While the obturator and method of the present invention has been described with reference to human patients, animal patients may in certain circumstances also benefit.

20 The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this

specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and
5 drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including
10 any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series
15 of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any
20 accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. An obturator for a bronchial tube or tubule of a human or animal lung comprising a blocking element and a securing element.
- 5 2. An obturator as claimed in claim 1, in which the two elements are separate components, the blocking element serving to seal the tube or tubule against the passage of fluid past the obturator when the obturator is disposed in a bronchial tube or tubule, and the securing element
10 serving to retain the blocking element in position in the tube or tubule.
3. An obturator as claimed in claim 1 or 2, in which the blocking element comprises a substantially cylindrical plug of biocompatible material.
- 15 4. An obturator as claimed in claim 3, in which the plug comprises resiliently deformable closed-cell foamed plastics material, such as PVC.
5. An obturator as claimed in any preceding claim, in which the securing element comprises a stent.

6. An obturator as claimed in claim 5, in which the stent has barbs to engage and retain the blocking element.
7. An obturator as claimed in claim 5 or 6, in which
5 the stent has anchors to retain the stent in a bronchial tube or tubule.
8. An obturator as claimed in claim 5, 6 or 7, in which the stent comprises a crown of surgical quality steel wire legs in zig-zag formation.
- 10 9. An obturator as claimed in claims 6, 7 and 8, in which said barbs and anchors depend from points of the crown.
10. An obturator as claimed in claim 8 or 9, in which the crown is closed in its circumference.
- 15 11. An obturator as claimed in claim 5, 6 or 7, in which the stent comprises a dome of surgical quality steel wire legs.
12. An obturator as claimed in claim 11, when dependent on claim 6, in which said barbs are formed on the ends of
20 said legs.

13. An obturator as claimed in claim 11 or 12, when dependent on claim 7, in which said anchors are formed on the end of said legs.

14. An obturator as claimed in any preceding claim,
5 further comprising a delivery device, which device comprises a delivery tube in which the obturator is received in a compressed state at a distal end thereof, a guide tube, which is capable of following a path under the guidance of a surgeon to a proposed delivery site in
10 a bronchial tube or tubule, and which has a passage to receive the delivery tube therealong, and release means to eject the obturator from the delivery tube and guide tube.

15. An obturator as claimed in claim 14, when dependent
15 on claim 5, in which the stent provides a low friction surface of the obturator to facilitate such ejection.

16. An obturator as claimed in claim 1, in which the blocking and securing elements are integrally formed from plastics material, and wherein the securing element
20 comprises adhered or fused anchor elements on the blocking element.

17. An obturator as claimed in claim 2, in which the securing element comprises a memory metal which is

released to its normal expanded shape by a physical parameter when it has been inserted at the proposed location.

18. An obturator as claimed in claim 17, in which said
5 physical parameter is the passage of electrical current through the securing means.

19. An obturator as claimed in claim 1 or 2, in which the blocking element comprises a balloon.

20. An obturator as claimed in claim 19, in which the
10 securing element comprises a stent, points of the stent being turned inwardly to captivate the balloon.

21. An obturator as claimed in claim 1 or 2, in which the blocking element comprises a diaphragm.

22. An obturator as claimed in claim 21, in which the
15 securing element comprises a domed stent secured at its point to the centre of the diaphragm, the legs of the stent pressing the diaphragm against the mucosa of a bronchial tube when inserted therein.

23. A method of treatment of emphysema or other lung
20 conditions or diseases in human or animal patients, the method comprising placing an obturator in a bronchial

tube or tubule of the patient so as to seal the tube or tubule against the passage of fluid past the obturator.

24. A method as claimed in claim 23, in which the obturator is put in place in a patient by use of a
5 delivery device for the obturator, which device is inserted through the mouth and airway of the patient until the proposed placement site is reached, whereupon the device is activated to release the obturator from the device.

10 25. A method as claimed in claim 23 or 24, which method employs an obturator of the type claimed in any of claims 1 to 22.

26. An obturator substantially as hereinbefore described with reference to any of the accompanying drawings.

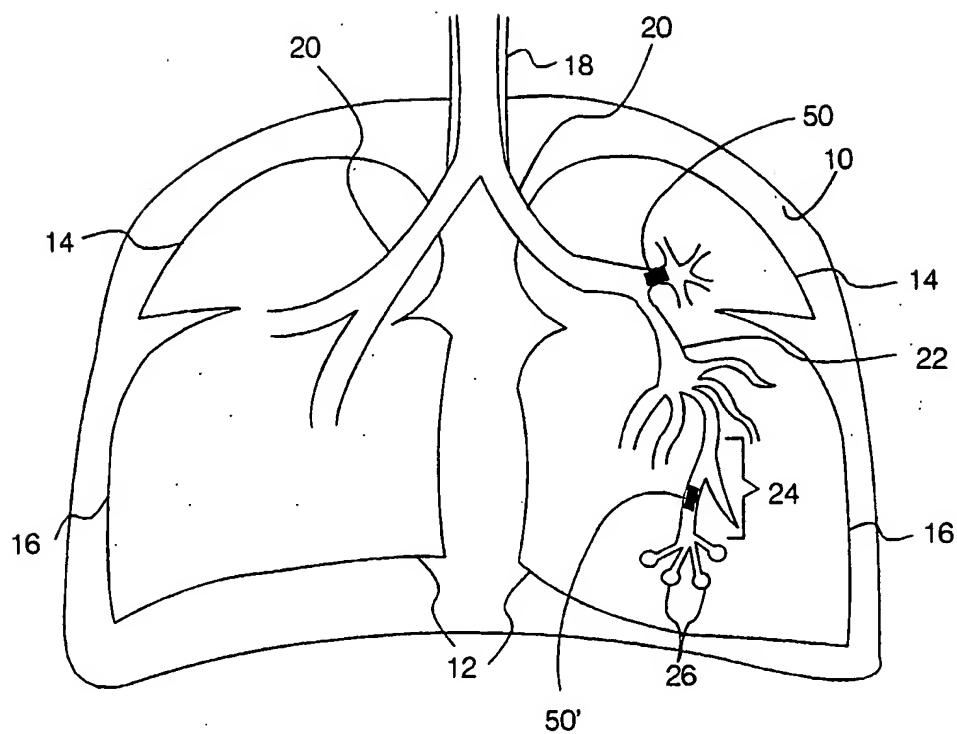


Fig. 1

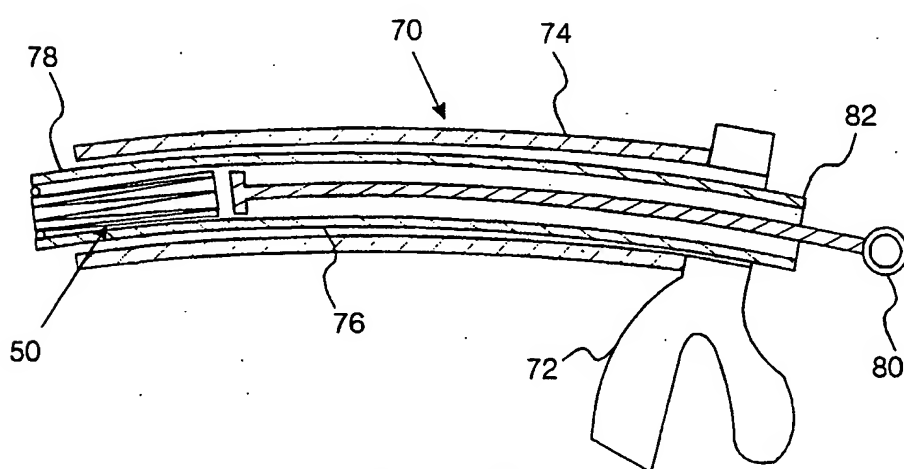


Fig. 2

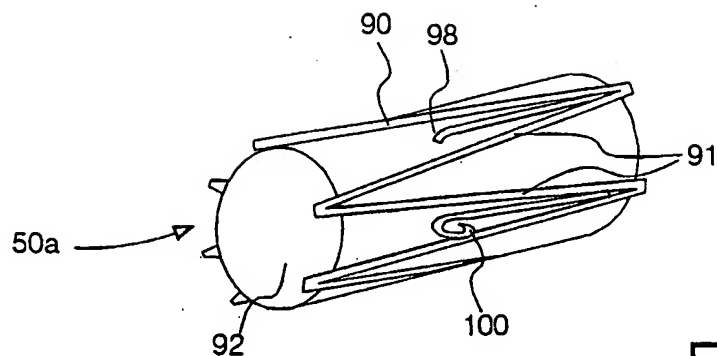


Fig. 3a

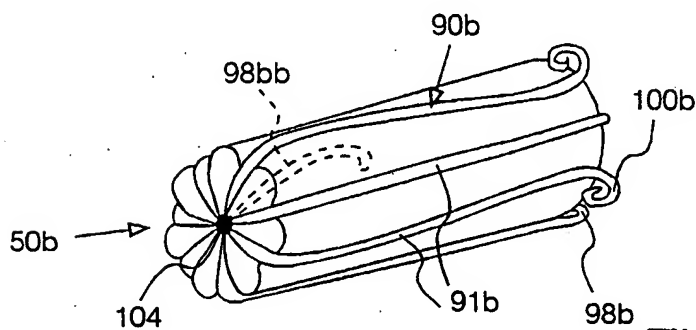


Fig. 3b

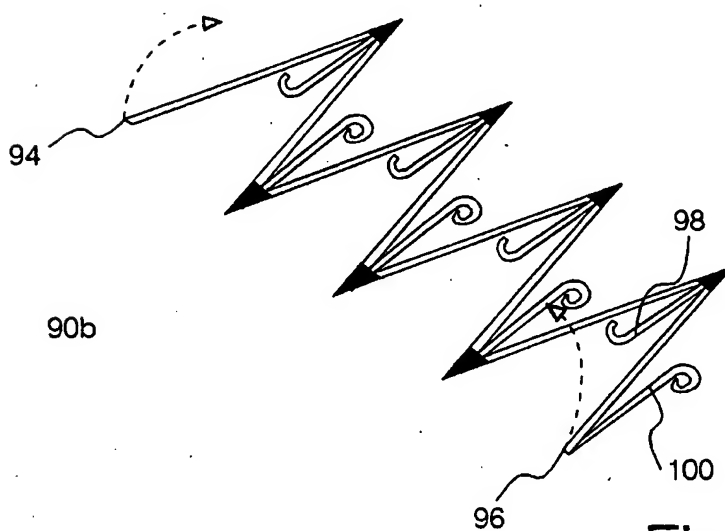


Fig. 3c

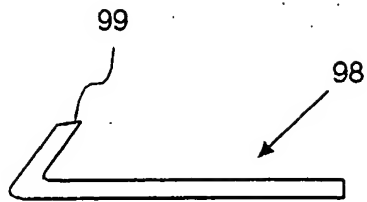


Fig. 4a

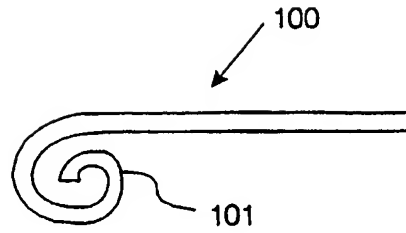


Fig. 4b

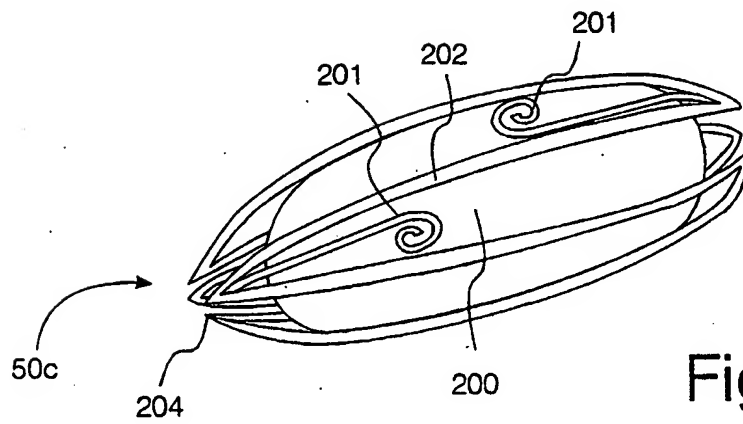


Fig. 5

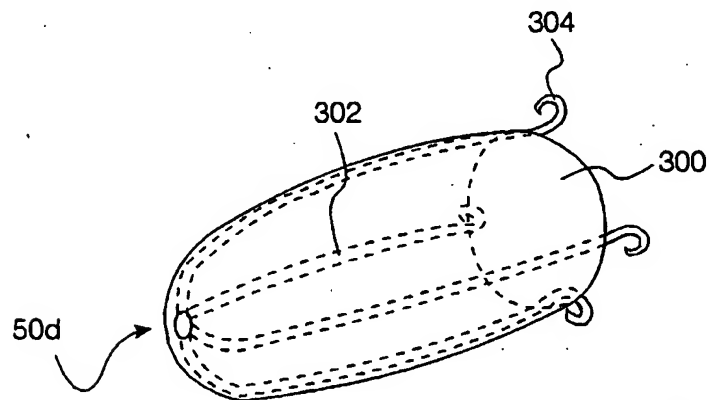


Fig. 6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00652

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B17/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 382 261 A (PALMAZ) 17 January 1995 see the whole document ---	1-3,5, 10,14, 15,21
X	DE 92 05 797 U (SCHMITZ-RODE ET AL.) 17 June 1992 see the whole document ---	1-3,5-7, 11-13, 17,21,22
X	WO 95 32018 A (TEIRSTEIN) 30 November 1995 see abstract; figures ---	1-3,19, 21
X	US 4 710 192 A (LIOTTA ET AL.) 1 December 1987 see abstract; figures see column 5, line 23-40 ---	1,2,5,7, 21
-/--		

☒ Further documents are listed in the continuation of box C.

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Date of mailing of the international search report

24/06/1998

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00652

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 204 218 A (STÖCKERT INSTRUMENTE GMBH) 10 December 1986 see column 2, line 14-49; figures ---	1-3, 16, 19
A	WO 94 26175 A (VITAPHORE CORPORATION) 24 November 1994 see abstract; figures ---	4, 14
A	US 5 246 445 A (YACHIA ET AL.) 21 September 1993 see abstract; figures see column 2, line 65-68 ---	1
A	DE 41 01 936 A (FISCHER ET AL.) 23 July 1992 see the whole document -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/00652

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00652

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5382261	A	17-01-1995	US 5656036 A	12-08-1997
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			EP 0723765 A	31-07-1996
			WO 9116005 A	31-10-1991
DE 4101936	A	23-07-1992	NONE	

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/10	A1	(11) International Publication Number: WO 98/49191 (43) International Publication Date: 5 November 1998 (05.11.98)
(21) International Application Number: PCT/US98/01711 (22) International Filing Date: 29 January 1998 (29.01.98) (30) Priority Data: 08/848,580 28 April 1997 (28.04.97) US (71) Applicant: THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US). (72) Inventors: COCHRANE, Charles, G.; 7782 Ludington Place, La Jolla, CA 92037 (US). REVAK, Susan, D.; 6561 Cascade Street, San Diego, CA 92122 (US). (74) Agents: FITTING, Thomas et al.; The Scripps Research Institute, TPC-8, 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NOVEL PULMONARY SURFACTANTS AND THERAPEUTIC USES, INCLUDING PULMONARY LAVAGE (57) Abstract <p>The present invention discloses useful surfactant molecules including polypeptides, proteins, and a variety of other organic molecules, as well as methods of making and using same. Surfactant compositions, including liposomal surfactant compositions, are also disclosed. Use of the surfactant molecules of the present invention in pulmonary lavage procedures for a variety of therapeutic applications is also disclosed, including the treatment of respiratory distress syndrome; the removal of inflammatory exudate from inflamed lung tissues; and the treatment of meconium aspiration syndrome in infants.</p>		

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NOVEL PULMONARY SURFACTANTS AND THERAPEUTIC USES,
INCLUDING PULMONARY LAVAGE

5

TECHNICAL FIELD

The present invention relates to surfactant molecules, including polypeptides, proteins, and a variety of other organic molecules, which are suitable for a variety of therapeutic uses, including the treatment of respiratory distress syndrome; the removal of inflammatory exudate from inflamed lung tissues; and the treatment of meconium aspiration syndrome in infants.

15 BACKGROUND

1. Meconium Aspiration Syndrome

Meconium-stained amniotic fluid is present in 5-20% of all births in the U.S. Each year, approximately 26,000 newborn infants in the U.S. develop Meconium Aspiration Syndrome (MAS) (Wiswell et al, Pediatr. Clin. North Am., 40:955-981, 1993; Gregory et al, J. Pediatrics, 85:848-852, 1974), involving progressive respiratory distress, hypoxia, hypercapnea, and acidosis requiring long-term ventilatory treatment. Severe cases require extracorporeal membrane oxygenation (ECMO) for survival (Bascik, Pediatr. Clin. North Am., 24:463-479, 1977; Moront et al, J. Thorac. Cardiovasc. Surg., 97:706-714, 1990; Toomasian et al, ASAID Trans., 34:140-147, 1988). Mortality rates vary between 4-12%. (See, e.g., Wiswell et al, Id., 1993; Coltar et al, Br. J. Obstet. Gynecol., 96:411-414, 1989; Davis et al, Am. J. Obstet. Gynecol., 151:731-736, 1985; Faleiglia, Obstet. Gynecol., 71:349-353, 1988).

Meconium aspiration can result in hypoxemia, vascular shunting and decreased compliance (Tyler et al, Pediatrics 62:454-459, 1978; Chen et al, Crit. Care. Med., 13:233-236, 1985). Experimental studies have shown that after inhalation of

- 2 -

meconium, collapse of subpleural alveoli takes place (Nieman et al, J. Appl. Physiol., 58:129-136, 1985; Clark et al, Pediatr. Res., 13:532, 1979) and gross and microscopic atelectasis develops (Clark et al, J. Pediatr., 110:765-770, 1987; Sun et al, J. Appl. Physiol., 77:1961-1971, 1994; Sun et al, Acta Paediatr., 82:182-189, 1993; Sun et al, Biol. Neonate, 63:96-104, 1993; Seo et al, Pediatr. Pathol., 10:539-548, 1990).

Atelectasis may result from mechanical obstruction (Tyler et al, Pediatrics, 62:454-459, 1978; Gooding et al, Radiology, 100:131-135, 1971; Tran et al, Pediatr. Res., 14:34-38, 1980) caused by the particulate meconium, a so-called chemical pneumonitis and meconium-induced dysfunction of surfactant. While mechanical obstruction may play a role in meconium-induced pulmonary injury, the use of filtered meconium, obviating mechanical obstruction, led to loss of pulmonary function and alveolar collapse (Chen et al, Crit. Care. Med., 13:233-236, 1985). This indicated a direct effect *in vivo* of the meconium on surfactant in the lung tissue. Surfactant extracts of atelectatic lung taken after meconium aspiration revealed poor surface tension in the Wilhelmy balance assay compared to those taken from expanded lung (Clark et al, J. Pediatr. 110:765-770, 1987), and in studies of adult rats and piglets, surfactant removed by lavage 60 min. after meconium aspiration showed poor surface tension properties (Sun et al, Acta Paediatr., 82:182-189, 1993; Davey et al, Ped. Res., 16:101-108, 1993).

A direct action of meconium on surfactant has been shown *in vitro*. A dose-dependent loss of surface activity of surfactant was produced by human meconium (Davey et al, Id., 1993; Moses et al, Am J Obstet Gynecol., 164:477-481, 1991). Both chloroform and aqueous extracts of meconium have been found active (Sun et al, Acta Paediatr., 82:182-189, 1993; Moses et al, Am J Obstet Gynecol., 164:477-481, 1991), although in a separate study

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(Clark et al, J. Pediatr., 110:765-770, 1987), only the organic extract was stated to be active.

Constituents of meconium that may contribute to alteration of the physical properties of surfactant include fatty acids, cholesterol, bile salts, bilirubin, and proteolytic enzymes (Clark et al, J. Pediatr., 110:765-770, 1987; Sun et al, Acta Paediatr., 82:182-189, 1993; Moses et al, Am J Obstet Gynecol., 164:477-481, 1991; Henderson et al, Can. J. Surg., 18:64-69, 1975; Lieberman, Gastroenterology, 50:183-190, 1966).

Another factor in the development of pulmonary dysfunction has been stated to be a "chemical pneumonitis" (Gregory et al, J. Pediatrics, 85:848-852, 1974; Bascik, Pediatr. Clin. North Am., 24:463-479, 1977; Tyler et al, Pediatrics, 62:454-459, 1978). While this dysfunction has not been clearly defined, it is presumed to follow interaction of components of meconium and the lung tissues. It is also difficult to distinguish a "chemical pneumonitis" from the inflammatory reaction that is stimulated by meconium aspiration (Tyler et al, Pediatrics, 62:454-459, 1978; Sun et al, J. Appl. Physiol., 77:1961-1971, 1994; Davey et al, Ped. Res., 16:101-108, 1993). Such an inflammatory reaction is characterized by edema, leukocyte accumulation and hemorrhage, developing 2-5 hours after exposure of the lungs to meconium and, according to a single report, increasing in severity over a 48 hour period (Tyler et al, Pediatrics, 62:454-459, 1978).

The components of meconium that initiate the inflammatory response, and the molecular mediating systems involved are poorly understood. Further, the effect of the inflammatory response on pulmonary function has not been determined.

With the evidence that surfactant function is impaired by meconium aspiration, some efforts have been directed toward therapeutic intervention with exogenous surfactant. Auten et

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al. treated 14 neonatal infants -- seven with MAS and seven with Respiratory Distress Syndrome (RDS) associated with pneumonia -- with calf lung surfactant extract and observed some improvement in lung function, but only minimal clearing of chest radiographs
5 (Auten et al, Pediatrics, 87:101-107, 1991). A majority of the patients required additional surfactant treatment. (Also see Davis et al, Pediatr. Pulmonol., 13:108-112, 1992).

Lotze et al. compared the response in 28 neonatal infants with MAS, pneumonia, hyaline membrane disease and idiopathic
10 pulmonary hypertension of the newborn to four bolus doses of bovine surfactant, with 28 similar infants in a control group, who were treated with air alone (J. Pediatr., 122:261-268, 1993). All the infant patients in that study, including those receiving boluses of bovine surfactant, required ECMO, although
15 the surfactant treatment was found to improve pulmonary mechanics and reduce time on ECMO. When the initial study was expanded to include 167 patients in the surfactant group and 161 patients in the air-placebo group, a decreased need for ECMO in the surfactant group was observed in a statistically significant
20 manner, *but only in those patients with the least severe disease*. No difference was found in time on ventilation, oxygen requirements, time to discharge, or incidence of pneumothorax, pulmonary interstitial emphysema and chronic lung disease (Lotze, Ped. Research, 39:#4 226A, 1996).

25 In a separate study, bolus administration of bovine surfactant to full-term neonates with either severe MAS (n=20) or severe RDS (n=29) produced increases in a/A ratio and a fall in Oxygen Index over a 6 hour period (Khammash et al, Pediatrics, 92:135-139, 1993). Most of the infants in both
30 groups required additional doses of the surfactant, however.

Results from studies addressing the efficacy of bolus surfactant treatment in animal models of MAS have been mixed.

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Sun et al. observed that intratracheal instillation of a slurry of human meconium in adult rats and newborn rabbits resulted in pulmonary injury that was diminished by bolus administration of porcine lung surfactant extract (Sun et al, J. Appl. Physiol., 5 77:1961-1971, 1994; Sun et al, Biol. Neonate, 63:96-104, 1993; Sun et al, Am. J. Crit. Care Med., 154:764-770, 1996).

Similarly, Smith claimed that bolus administration of surfactant brought about an improvement in lung function in animal models of MAS. (See Smith et al, "Exogenous surfactant in the 10 treatment of the meconium aspiration syndrome (MAS)," presented at the 9th Annual High Frequency Ventilation of the Newborn meeting, Snowbird, Utah, April 2, 1992).

However, when Wiswell et al. studied two different surfactants in a piglet model of MAS, they failed to observe 15 differences from controls in mean airway pressures and a/A ratio over a 6 hour period (Wiswell et al, Pediatrics Res, 36:494-500, 1994). Histologic observations were also similar in treated and control groups. Therefore, studies to date suggest that the results are equivocal when bovine- or porcine-derived surfactant 20 preparations are administered, particularly when administered as a bolus.

In view of the variable and limited efficacy of bolus surfactant strategies in the treatment of MAS, attention has recently been focused on approaches employing pulmonary lavage. 25 Limited studies using piglets or rabbits as MAS models, wherein the animals' meconium-injured lungs were treated with lavage solutions. The investigators claimed that lung function improved when surfactant was administered, but not when saline lavages alone were used (Paranka et al, Pediatr Res, 31:625-628, 30 1992; and Ohama et al, Acta Paediatr Japonica, 33:236-238, 1994). (See also Balaraman et al, Am. J. Respir. Crit. Care Med., 153:1838-1843, 1996). Similarly, two human infants with

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severe MAS, both destined for ECMO, were treated with repeated saline lavage, 10 ml/kg, followed by instillation of bovine surfactant. Both infants responded rapidly with an increase in a/A and clearing of chest radiographs in 4-5 hours (Ibara et al, 5 Acta. Paed. Japonica, 37: 64-67, 1995).

2. Acute Respiratory Distress Syndrome (ARDS)

ARDS is an inflammatory disease of the lung, occurring in all ages of human beings, involving approximately 50,000 - 10 100,000 people in the United States per year. As the disease progresses, pulmonary function fails, requiring mechanical ventilation, and approximately 40-50% of patients die with the disease.

Many initiating factors lead to the development of ARDS, 15 including aspiration of injurious substances such as gastric contents, inhalation of noxious fumes, including smoke or NO₂, pneumonia, pulmonary contusion, trauma, multiple transfusions, burns, sepsis, pancreatitis, etc. The early disease is marked by an edematous response in the lung, with accumulation of 20 neutrophils, leading to the development of chronicity in a week with fibrin deposits and collagen production. Injury to epithelial cells is observed in the early phase together with interstitial edema.

During the development of injury, intrinsic surfactant is 25 degraded, losing function, and atelectatic collapse of the alveoli is prominent.

Complications are prominent: failure of peripheral organs, including kidneys, liver, gastrointestinal tract and the arterial system is common. Mortality rises in proportion to the 30 number of systems undergoing failure. There is no specific therapy for this disease.

In view of the variability in efficacy achieved by using

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exogenous surfactants -- particularly when the surfactant is derived from non-human sources or when the surfactant is given as a bolus -- and in view of the somewhat equivocal results achieved when standard lavage methods are used, alternative
5 therapeutic modalities and formulations are clearly needed. Therefore, the compositions and methods disclosed herein provide a very real improvement over therapies and compositions described in the art.

10 BRIEF DESCRIPTION OF THE INVENTION

It has now been discovered that in treating the inflamed lung with pulmonary surfactant, a combination of three conditions provides superior therapy for a variety of medical diseases marked by respiratory distress as follows:

15 (1) dilute surfactant is administered to the lung by a lavage technique to remove injurious material and/or inflammatory exudate, to expand the lung and to improve pulmonary function;

(2) the dilute surfactant administration and monitoring of
20 the course of pulmonary function is followed under regulated positive end-expiratory pressure; and

(3) the dilute surfactant lavage fluid is removed from the lung using timed short intervals of suctioning.

The present invention discloses a wide variety of
25 surfactant molecules which may be formulated, prepared and utilized as surfactant compositions, particularly as dilute surfactant in a lavage composition, as disclosed herein.

In particular, the present invention discloses compositions and methods useful in the treatment of respiratory distress,
30 such as Acute Respiratory Distress Syndrome (ARDS), in general, or Meconium Aspiration Syndrome (MAS) suffered by many newborn infants, in particular. The dilute surfactant lavage can also

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be conducted to treat respiratory distress (e.g., RDS) in a mammal which may be associated with pulmonary inflammation, pulmonary infection, sepsis, pulmonary trauma, cranial or body trauma, pancreatitis, aspiration of gastric contents, heated
5 vapor inhalation, noxious vapor inhalation, acute hypoxemia, fetal circulation, congenital diaphragmatic hernia, pneumonia, multiple transfusions, and the like conditions.

In one embodiment, the invention contemplates a method for pulmonary lavage of a mammal comprising the steps of:

- 10 a) applying gas positive end-expiratory pressure (PEEP) with a ventilator into a lung section of the mammal at a regulated pressure, preferably from about 4 to 20 cm water;
- b) instilling a lavage composition containing dilute surfactant in a pharmaceutically acceptable aqueous medium into
15 one or more lobes or sections of the lung; and
- c) removing the resulting pulmonary fluid from the lung using short intervals of tracheo-bronchial suction, preferably using a negative pressure of about 20 to 100 mm mercury.

20 Typically, the PEEP is applied for a preselected time period prior to instilling step (b), preferably up to about 30 minutes, and in addition PEEP is typically applied continuously during steps (b) and (c) and for a preselected time period after removing step (c), preferably up to about 6 hours.

25 The invention can be practiced on newborn infants, infants, juveniles and adults, and is suitable for treating respiratory distress in any mammal, although it is a particularly important procedure in humans due to the extent of ARDS in human populations.

30 In preferred embodiments, ventilator PEEP levels are maintained at 4-15 cm water, preferably 6-9 cm water when treating newborn infants, and preferably about 6-12 cm water

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when treating babies, juveniles and adults. These levels have been found to facilitate lung expansion during the treatment, increasing therapeutic surfactant contact onto the alveoli and in particular to increase the rate of removal of fluids and
5 inhibitors of surfactant function from the lung during the recovery phase. The gas applied may optionally be enriched in oxygen, i.e, from about 21 to 100% O₂.

A dilute surfactant is typically present in the lavage composition at 0.1 - 50 mg per ml, preferably about 0.5 - 20 mg
10 per ml. The lavage composition is typically instilled in a volume of about 4-60 ml per kilogram, preferably about 8-30 ml per kilogram.

The short interval of suction to remove pulmonary fluids, including the instilled lavage composition, is important to
15 minimize the drop in arterial oxygen that occurs during the suction step. A typical suctioning interval is about 2 to 120 seconds, and preferably is 5 to 20 seconds. The short suction removal step can be repeated as needed, typically 2-3 times, usually with an interval between removal steps of from about 5
20 seconds to 5 minutes, depending upon the condition of the patient.

In addition, the combination of instilling and removing steps can be repeated, as multiple "washes", up to 1 to 5 times, as needed.

25 Any of a variety of compounds, agents and molecules can be utilized as the active ingredient having surfactant activity in the lavage composition, so long as the composition is formulated as a dilute surfactant as described herein. The surfactant can comprise a substantially isolated natural pulmonary surfactant
30 (SP) protein, or fragments thereof, a synthetic pulmonary surfactant, including peptide, organic mimetics and the like. Alternatively, the surfactant can be protein or peptide-free.

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A preferred synthetic pulmonary surfactant comprises one or more phospholipids and a protein or polypeptide, in which the polypeptide, when admixed with a phospholipid, forms a synthetic pulmonary surfactant having a surfactant activity greater than
 5 the surfactant activity of the phospholipids alone. An exemplary polypeptide comprises at least 10 amino acid residues and no more than about 60 amino acid residues, including a sequence having alternating hydrophobic and hydrophilic amino acid residue regions represented by the formula $(Z_a U_b)_c Z_d$,
 10 wherein:

Z is a hydrophilic amino acid residue independently selected from the group consisting of R, D, E and K;

U is a hydrophobic amino acid residue independently selected from the group consisting of V, I, L, C and F;

15 a has an average value of about 1 to about 5;
 b has an average value of about 3 to about 20;
 c is 1 to 10; and
 d is 0 to 3.

Particularly preferred are surfactant compositions
 20 comprising a polypeptide having an amino acid residue sequence represented by the formula:

KLKKLKKKKLKKKKLKKK;

or having an amino acid residue sequence selected from the group consisting of:

25 KLKKLKKKKLKKKKLKKK,
 KKKKKKKKKLKKKKKKKKL, and
 KKKKKKKKKKKLKKKKKKK;

or having an amino acid residue sequence selected from the group consisting of:

30 DKKKDKKKDKKKDKKKD,
 RKKKRLKKRLKKRLKKR,
 RKKKKKKRKKKKKKR,

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RRLLLLLLLRRLLLLLLLLRRL,
RLLLLCLLLRLLLLCLLLR,
RLLLLCLLLRLLLLCLLLRLL, and
RLLLLCLLLRLLLLCLLLRLLLR.

5 A synthetic pulmonary surfactant used in the present invention typically contains a polypeptide:phospholipid weight ratio in the range of about 1:7 to about 1:1,000. A preferred phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine
10 (dipalmitoylphosphatidylcholine, DPPC);
phosphatidyl glycerol (PG); and
an admixture of DPPC and PG in a weight ratio of about 3:1.
In preferred embodiments, the synthetic pulmonary surfactant further contains palmitic acid.

15 Therefore, in various preferred embodiments of the present invention, a wide variety of surfactant polypeptides, compositions, formulations, and methods of making and using same are disclosed.

20 BRIEF DESCRIPTION OF THE DRAWINGS

The importance of three treatment conditions for practicing the claimed methods are illustrated in the Figures described below:

(1) Pulmonary lavage with dilute surfactant substantially
25 increases pulmonary function (Figures 2, 4, 6, 8, 9, and 12A). This improvement in function follows removal of injurious material (Figure 5) and of inflammatory exudate (Figure 10) by the lavage procedure. The surfactant lavage also inhibits return of the inflammatory process in the lungs (Figure 11).

30 (2) The important role of positive end-expiratory pressure (PEEP) in surfactant-induced expansion of the lung (Figure 12) and in diminishing the fall in O₂ saturation (Figure 13) during

the lavage procedure.

(3) The importance of timed short intervals of negative-pressure suctioning on diminishing the fall in O_2 saturation (Figure 14).

5 Figure 1 illustrates the Merrifield method, which method may be used in the synthesis of a surfactant peptide of the present invention as described in Example 1.

Figure 2 compares the effect of administration of KL_4 -containing surfactant versus non-peptide surfactant on lung
10 function in preterm infant monkeys as described in Example 6. The ratio of arterial to alveolar oxygen tension (a/A) was measured in preterm rhesus monkeys treated to a dose of KL_4 -surfactant (solid bars) or treated with a non-peptide surfactant (hatched bars) periodically over about 11 hours after cesarian
15 delivery. Each bar represents the mean \pm SEM of all available data points within 0.5 hours of the listed time. Asterisks indicate significant statistical differences between the groups.

Figure 3 illustrates the PaO_2 response of rabbits receiving intratracheal meconium as described in Example 5. Adult rabbits
20 were given 7.5 ml/kg of saline (open circles, $n=3$) or a 25 mg/ml slurry of human meconium (closed squares, $n=7$) at $t = 0$ hours. PaO_2 was followed for 5 hours. Data are expressed as mean \pm SEM. The time points of -0.5 and 0 hours are the mean values obtained pre-dosing at times varying from -0.77 to -0.03 hours; remaining
25 time points are those nearest to the stated times. $p < 0.05$ for all time points ≥ 1.0 hours.

Figures 4A-4D show compliance curves, expressed as change in change in air volume (ml/kg) as a function of pressure (cm H_2O) as described in Example 5. Compliance curves are shown for
30 four representative rabbits that received 187.5 mg/kg human meconium instilled intratracheally immediately after compliance assessment at $t = 0$ hr. Figure 4A shows an animal that received

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no further treatment, while Figure 4B shows an animal that at $t = 1.1$ hr was lavaged 3 times using 2 mg/ml and once using 15 mg/kg KL_4 -Surfactant (20 ml/kg each). Figure 4C shows a meconium-injured animal that was lavaged 3 times with saline (20 ml/kg); and Figure 4D shows an animal that received a bolus instillation of KL_4 -Surfactant (100 mg/kg) at 1.1 hrs. For each animal, compliance data are shown for time points immediately before meconium was administered (open circles), approximately 0.9 hrs after meconium (before rescue treatment, open squares), and approximately 5.4 hrs after meconium (4 hrs after rescue treatment, solid triangles). Each animal is representative of animals in its treatment group.

Figure 5 illustrates the removal of meconium by lavage with KL_4 -Surfactant as described in Example 5. Human meconium (187.5 mg/kg) was instilled into the lungs of adult rabbits. Approximately 1.1 hours later, each animal was lavaged at least 3 times with 20 ml/kg of KL_4 -Surfactant at a concentration of 2 mg/ml. Data are shown as the mean \pm SEM percent of instilled meconium recovered in each lavage for six animals.

Figure 6 illustrates changes in pulmonary function in meconium-injured rabbits following lavage with dilute KL_4 -Surfactant as described in Example 5. Rabbits were injured with 187.5 mg/kg meconium instilled intratracheally at $t = 0$. Approximately 1 hour later, 12 rabbits were lavaged 2-4 times with dilute KL_4 -Surfactant (2-5 mg/ml) using 20 ml/kg followed by one lavage with a higher concentration (10-15 mg/ml) of the surfactant (solid squares). Five control animals were lavaged 3-4 times with 20 ml/kg of saline (open circles). Data are expressed as mean \pm SEM. The time points of -0.5 and 0 hours are the mean values obtained pre-dosing at times varying from -1.0 to -0.03 hours; remaining time points are those nearest to the stated time. $p < 0.05$ for all time points > 1 hour.

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Figure 7 illustrates changes in pulmonary function in meconium-injured rabbits following a bolus instillation of KL₄-Surfactant as described in Example 5. Five rabbits were injured with 187.5 mg/kg meconium instilled intratracheally at t = 0.

5 Approximately 1.1 hours later, each animal was given 100 mg/kg KL₄-Surfactant in a volume of 3.33 ml/kg. Data are expressed as the mean \pm SEM. The time points of -0.5 and 0 hours are the mean values obtained pre-dosing at times varying from -.15 to -0.03 hours; remaining time points are those nearest to the

10 stated time.

Figure 8 illustrates the effect of treating meconium-injured newborn rhesus monkeys with KL₄-Surfactant lavage as described in Example 5. Seven newborn rhesus monkeys were given meconium (656 mg/kg mean quantity) into the tracheal fluid at

15 birth. Six were treated at a mean time of 2.8 hours with 3 or 4 lavages of KL₄-Surfactant diluted to 2 mg/ml, followed by either lavage using KL₄-Surfactant at 15 mg/ml or a bolus of 100 mg at 30 mg/ml; one remained untreated and served as a control animal. Data shown are the mean \pm SEM values for the a/A ratio at the

20 indicated time points. Time 0 is defined as the start of the lavage procedure.

Figure 9 illustrates the pulmonary function measured as PaO₂ in adult rabbits partially depleted of intrinsic surfactant by treatment with bacterial LPS-induced lung injury as a model of

25 ARDS as described in Example 7. Following instillation of 0.75 ug/kg bacterial LPS, adult rabbits were given lavage washes containing dilute KL₄-surfactant containing 5 mg/ml surfactant or were untreated. PaO₂ was followed prior to LPS and thereafter for 8 hours. Data are expressed as mean \pm SEM.

30 Figures 10A through 10D illustrate a bar graph in four panels showing the amount of four components of inflammatory exudate present in sequential lavage washes following LPS injury

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in the adult rabbit as described in Example 7. First, second and third lavage washes are shown in each panel indicating the amount of component present in each wash.

Figures 11A through 11D illustrate a bar graph in four panels showing the amount of four components in inflammatory exudate present in pulmonary wash 3 hours after treatment with dilute surfactant following LPS injury in the adult rabbit as described in Example 7. Three hours after the surfactant lavage treatment described in Figure 10, a pulmonary saline wash was collected from the lung of control and surfactant-treated rabbits. The contents of inflammatory components were analyzed in each, and are shown in each panel indicating the amount of component present in each wash.

Figure 12, in two panels Figure 12A and Figure 12B, illustrates the effect of elevated PEEP levels on improvement of lung function by dilute surfactant lavage in meconium-injured pigs as described in Example 8. Meconium-injured pigs were treated with surfactant lavages at the time points indicated (arrows) at PEEP of 8 cm water (Figure 12A) or PEEP of 6 cm water (Figure 12B). Lung function was measured by following PaO_2 over time during meconium installations, during surfactant lavage, and for approximately 2-4 hours after the lavage procedure.

Figure 13 illustrates the effect of PEEP on O_2 saturation (SaO_2) over time during the surfactant lavage procedure as described in Example 8. At PEEP of 8 cm water, the loss of O_2 saturation is considerably less than the loss that occurs when PEEP is maintained at 6 cm water.

Figure 14, in two panels Figure 14A and Figure 14B, illustrates the effect of the length of time of the suction interval on improvement of lung function by dilute surfactant lavage in meconium-injured pigs as described in Example 8.

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Meconium-injured pigs were treated as described in Example 8 with a lavage and suction using negative pressure for 10 seconds (Figure 14A) or about 60 seconds (Figure 14B). Lung function was measured by following SaO₂ (saturated O₂) over time during 5 meconium installations, during surfactant lavage, and after the lavage procedure.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

10 Amino Acid: In various preferred embodiments, amino acid residues identified as useful are in the natural L-configuration. As disclosed hereinbelow, however, D-amino acids, substituted amino acids (e.g., amino acids with modified R groups) amino acid metabolites and catabolites, amino acids 15 with "retro" backbones, and amino acid mimics or analogs are also contemplated for use in -- and are thus encompassed by -- the present invention..

In keeping with standard polypeptide nomenclature, J. Biol. Chem., 243:3557-59, 1969, abbreviations for the more common 20 amino acid residues are as shown in the following Table of Correspondence:

Table of Correspondence

	<u>Symbol</u>		<u>Amino Acid</u>
	<u>1-Letter</u>	<u>3-Letter</u>	
25	Y	Tyr	L-tyrosine
	G	Gly	glycine
	F	Phe	L-phenylalanine
	M	Met	L-methionine
30	A	Ala	L-alanine
	S	Ser	L-serine
	I	Ile	L-isoleucine
	L	Leu	L-leucine

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	T	Thr	L-threonine
	V	Val	L-valine
	P	Pro	L-proline
	K	Lys	L-lysine
5	H	His	L-histidine
	Q	Gln	L-glutamine
	E	Glu	L-glutamic acid
	W	Trp	L-tryptophan
	R	Arg	L-arginine
10	D	Asp	L-aspartic acid
	N	Asn	L-asparagine
	C	Cys	L-cysteine
	X	Xaa	Unknown/other

15 It should be noted that, unless otherwise indicated, the amino acid residue sequences represented herein by formulae have a left to right orientation in the conventional direction of amino-terminus to carboxy-terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino

20 acids listed in the Table of Correspondence and modified and unusual amino acids, such as those listed in 37 C.F.R. §1.822(b)(4), and incorporated herein by reference. The phrase "amino acid residue" is also broadly defined to include D-amino acids, substituted amino acids (e.g., amino acids with modified

25 R groups), modified amino acids (e.g., amino acid metabolites, catabolites, and amino acids with "designed" side chains), and amino acid mimics or analogs.

 Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence generally

30 indicates a bond to a radical such as H and OH (hydrogen and hydroxyl) at the amino- and carboxy-termini, respectively, or a further sequence of one or more amino acid residues. In addition, it should be noted that a virgule (/) at the right-

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hand end of a residue sequence indicates that the sequence is continued on the next line.

Pharmaceutically acceptable is a term that refers to molecular entities and compositions that do not produce an
5 allergic or similar untoward reaction when administered to a human.

Polypeptide and peptide are terms used interchangeably herein to designate a linear series of no more than about 60 amino acid residues connected one to the other by peptide bonds
10 between the alpha-amino and carboxy groups of adjacent residues.

Protein is a term used herein to designate a linear series of greater than about 60 amino acid residues connected one to the other as in a polypeptide.

Surfactant activity. As used herein, the term refers
15 to the ability of any substance, such as an organic molecule, protein or polypeptide -- when combined with lipids, either alone or in combination with other organic molecules, to lower surface tension at an air/water interface. The measurement can be made with a Wilhelmy Balance or pulsating bubble
20 surfactometer by an *in vitro* assay. See, for example that of King et al, Am. J. Physiol. 223:715-726 (1972), or the assay illustrated herein, which utilizes a measurement of surface tension at an air-water interface when a protein or polypeptide is admixed with a phospholipid. In addition, *in vivo*
25 measurements of increases of compliance or airflow at a given pressure of air entering the lung can be readily made, such as in the assay of Robertson, Lung, 158:57-68 (1980). In this assay, the sample to be assessed is administered through an endotracheal tube to fetal rabbits or lambs delivered
30 prematurely by Caesarian section. (These "preemies" lack their own PS, and are supported on a ventilator.) Measurements of lung compliance, blood gases and ventilator pressure provide

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indices of activity. *In vitro* assays of surfactant activity, which is assessed as the ability to lower the surface tension of a pulsating bubble, and *in vivo* assays utilizing fetal rabbits, as reported herein, are described in detail by Revak et al, Am. Rev. Respir. Dis., 134:1258-1265 (1986).

B. Pulmonary Surfactants -- Overview

Naturally-occurring pulmonary surfactant is a complex mixture of lipids and proteins that promotes the formation of a monolayer at the alveolar air-water interface and, by reducing the surface tension, prevents collapse of the alveolus during expiration. Premature infants, and occasionally full term neonates, may lack sufficient endogenous surfactant for normal lung function. This can give rise to a condition termed respiratory distress syndrome (RDS) which may necessitate mechanical ventilation and administration of hyperbaric oxygen. Such intervention, unfortunately, can produce permanent damage to lung tissue and may cause retinopathy of prematurity (ROP) leading to blindness.

Pulmonary surfactant (PS) lines the alveolar epithelium of mature mammalian lungs. Natural PS has been described as a "lipoprotein complex" because it contains both phospholipids and apoproteins that interact to reduce surface tension at the lung air-liquid interface. Natural surfactant contains several lipid species of which dipalmitoyl phosphatidylcholine (DPPC) is the major component together with phosphatidylglycerol (PG) and palmitic acid (PA). At least three specific proteins are also associated, termed SP-A, SP-B and SP-C. Of these three, SP-B and SP-C are distinct, low molecular weight, relatively hydrophobic proteins that have been shown to enhance the surface-active properties of surfactant phospholipid mixtures. It is believed that they facilitate transfer of lipids from the

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bulk phase lamellar organization to the air-water interface and also stabilize the lipid monolayer during expiration. The structure of SP-B (which is alternatively referred to as SP18) is unusual in that charged amino acids (predominantly basic) are
5 located at fairly regular intervals within stretches of otherwise hydrophobic residues. For the domain consisting of residues 59-80 of the native SP-B sequence, these charged groups have been shown to be necessary for biological activity. In addition, natural and synthetic peptides which are modeled on
10 this hydrophobic-hydrophilic domain when combined with DPPC and PG exhibit good surfactant activity.

Surfactant is stored in lung epithelial cells in the form of lamellar bodies and, following export, it undergoes a structural transition to form tubular myelin before giving rise
15 to a monolayer at the air-water interface. It has been proposed that surfactant proteins SP-A, -B and -C may facilitate these structural transitions and stabilize the lipid monolayer during expansion and contraction of the alveolus; however, an understanding of lipid-protein interactions at the molecular
20 level is presently lacking. The present invention, therefore, has important implications not only with respect to the treatment of RDS in infants as well as adults, but also because of the insight it may provide into lipid-protein interactions in general.

25 Several exogenous surfactant formulations are currently used in the treatment of infant RDS. While these have reduced morbidity and mortality, continual improvements are needed. In particular, because of the complications that can arise due to mechanical ventilation and administration of hyperbaric oxygen,
30 the sooner normal lung function can be established in a premature infant the more favorable will be the clinical outcome.

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Consistent with the foregoing, important characteristics in an exogenous surfactant include the ability to spread rapidly to the alveoli following administration and the ability to maintain a stable monolayer at the alveolar air-water interface so that repeated treatment is not required. Thus, various compounds and compositions that are useful in the preparation of superior exogenous surfactants are disclosed herein.

C. Surfactant Compositions

A surfactant composition of the present invention can contain any of a variety of pharmaceutically acceptable compounds having surfactant activity to form a pulmonary surfactant (PS) useful in the treatment of respiratory distress syndrome. Typically a surfactant composition has admixed therein one or more phospholipids. Phospholipids useful in forming alveolar surfactants are well known in the art. See, Notter et al, Clin. Perinatology, 14:433-79 (1987), for a review of the use of both native and synthetic phospholipids for surfactants.

The surfactant compositions of this invention that are prepared using a protein, a polypeptide, an amino acid residue-containing molecule, or another organic molecule of the present invention having surfactant activity (collectively, "surfactant molecules"), that can include one or more phospholipids, are well suited for the treatment of Respiratory Distress Syndrome (RDS). Such surfactant compositions typically range from dilute to concentrated, depending upon the intended use as described further herein. Thus a surfactant composition can contain from as little as about 0.05 to almost 100 weight percent lipid, so long as the resulting composition has surfactant activity. By weight percent is meant the percentage of a compound by weight in a composition by weight. Thus, a composition having 50

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weight percent lipid contains, for example, 50 grams lipid per 100 grams total composition. Typically, a surfactant composition contains 0.1 to 50 weight percent lipid, although higher concentrations of lipid can be used for "bolus" methods and for preparing more dilute surfactant compositions from a concentrated stock. Exemplary surfactant compositions containing both phospholipid and a surfactant molecule can contain, therefore, 0.1, 1, 10, 50, 80, to almost 100 weight percent lipid and about 50, 20, 10, to less than 1 weight percent surfactant molecule.

The surfactant composition is prepared by admixing a solution of a surfactant molecule with a suspension of liposomes, or by admixing the surfactant molecule with a suspension of liposomes, or by admixing the surfactant molecule and phospholipids directly in the presence of organic solvent.

Liposomal surfactant compositions of the present invention are generally sterile liposome suspensions containing a surfactant molecule of the present invention which has been combined with the lipids and a free fatty acid in an organic solvent system, dried, and then rehydrated. Because of the large variety of compounds and substances which have surfactant activity, it is to be understood that a surfactant composition useful in the present invention can be free from detectable protein or polypeptide, and contains only phospholipids, aqueous medium and/or buffers.

In various preferred embodiments of the present invention, pulmonary surfactants effective in treating RDS comprising an effective amount of a surfactant molecule admixed with a pharmaceutically acceptable phospholipid are disclosed. In one preferred embodiment, the surfactant molecule is a polypeptide or protein; in others, the surfactant molecule is an organic molecule displaying surfactant activity which may comprise amino

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acid residues, modified amino acids, amino acid derivatives, amino acid analogs, and the like molecules, or other organic molecules mimicking that activity.

While methods for determining the optimal polypeptide:phospholipid weight ratios for a given polypeptide-phospholipid combination are well known, we have determined that therapeutically effective ratios are in the range of about 1:5 to about 1:10,000, preferably about 1:7 to about 1:5,000, more preferably about 1:10 to about 1:1000, and more preferably about 1:15 to about 1:100.

The lipid portion of a surfactant composition of the present invention is preferably about 50 to about 90, more preferably about 50 to about 75, weight percent dipalmitoylphosphatidylcholine (DPPC) with the remainder comprising unsaturated phosphatidyl choline, phosphatidyl glycerol (PG), triacylglycerols, palmitic acid, sphingomyelin or admixtures thereof.

Phospholipids useful in forming the present liposomal surfactant compositions are well known in the art. (See, e.g., Notter et al, Clin. Perinatology, 14:433-79, 1987, for a review of the use of both native and synthetic phospholipids for surfactants.) Methods and materials useful in the preparation of preferred surfactant compositions as disclosed herein are also described in the Examples that follow.

A pulmonary surfactant of the present invention is generally prepared by admixing a solution of a subject polypeptide with a suspension of liposomes or by admixing the subject polypeptide (or other organic surfactant molecule) and lipids directly in the presence of organic solvent. The solvent is then removed by dialysis or evaporation under nitrogen and/or exposure to vacuum.

A pulmonary surfactant composition is preferably formulated

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for endotracheal administration, e.g., typically as a liquid suspension, as a dry powder "dust", or as an aerosol. Those of skill in the art will appreciate that surfactant compositions of the present invention may be formulated for a variety of uses and methods of administration including, without limitation, liquid suspensions or aerosols which may be used for lavage.

For example, a surfactant (surfactant molecule-lipid micelle) may be suspended in a liquid with a pharmaceutically acceptable excipient such as water, saline, dextrose, glycerol and the like. A surfactant-containing therapeutic composition can also contain small amounts of non-toxic auxiliary substances such as pH buffering agents, including sodium acetate, sodium phosphate, and the like. To prepare a surfactant in dust form, a surfactant is prepared as described herein, then lyophilized and recovered as a dry powder.

If it is to be used in aerosol administration, a subject surfactant is supplied in finely divided form along with an additional surfactant and propellant. Typical surfactants which may be administered are phospholipids and esters. However, it is preferred, in the present case, to utilize the other components of the surfactant complex, DPPC and PG. Useful propellants are typically gases at ambient conditions, and are condensed under pressure. Lower alkane and fluorinated alkane, such as Freon, may be used. The aerosol is packaged in a container equipped with a suitable valve so that the ingredients may be maintained under pressure until released.

To prepare a liposomal surfactant composition, the surfactant molecule or polypeptide molecule is dissolved in an organic solvent that maintains the molecule in its monomeric, substantially aggregate-free form. Preferred such solvents can be polar or non-polar and exhibit solubility parameter δ values in the range of about 9 to about 15 (cal \cdot cm 3) $^{1/2}$ or about 9

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Hildebrand units (H) to about 15H.

Particularly preferred solvents are the hydrogen bonded solvents such as the C₁ to C₄ aliphatic alcohols, i.e., methanol ($\delta = 14.5H$), ethanol ($\delta = 12.7H$), n-propanol ($\delta = 11.9H$), iso-
5 propanol ($\delta = 11.5H$), n-butanol ($\delta = 11.4H$), iso-butanol ($\delta = 10.8H$), etc. Among halogenated solvents particularly preferred are trifluoroethanol (TFE) and chloroform ($\delta = 9.3H$). Mixtures or blends of aliphatic alcohols and halogenated solvents can be utilized as well.

10 In a preferred method for producing a liposomal surfactant composition, the polypeptide or other surfactant molecule is dissolved in the organic solvent together with the phospholipids, and the resulting solution is combined with an aqueous buffer solution. The resulting suspension is then
15 dialyzed to remove the organic solvent. Alternatively, the organic solvent can be removed by evaporation and vacuum. The dried lipid/polypeptide mixture thus produced is rehydrated in an aqueous buffer system to produce the liposomes.

The present invention also contemplates a variety of
20 surfactant compositions, particularly liposomal surfactants. Thus, in one preferred embodiment, the invention discloses a liposomal surfactant composition prepared from a polypeptide comprising about 10 amino acid residues and no more than about 60 amino acid residues and is constituted by alternating
25 groupings of charged amino acid residues and uncharged amino acid residues, and a pharmaceutically acceptable phospholipid, wherein the polypeptide is present in an amount sufficient to increase the surfactant activity of the composition above that of the phospholipid.

30 In another preferred variation, a surfactant composition of the present invention comprises a surfactant molecule constituted by alternating groupings of charged and uncharged

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residues; the residues may be amino acids, modified amino acids, amino acid analogs or derivatives, and the like. Molecules having surfactant activity as disclosed herein are especially preferred for use in compositions of the present invention.

5 In various preferred embodiments of the present invention, as noted previously, surfactant compositions also comprise one or more phospholipids. The polypeptide:phospholipid weight ratio is in the range of about 1:7 to about 1:1,000 in various preferred surfactant compositions of the present invention.

10 Suitable phospholipids are preferably selected from the following group: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dipalmitoylphosphatidylcholine, DPPC); phosphatidyl glycerol (PG); and an admixture of DPPC and PG in a weight ratio of about 3:1.

15 The surfactant compositions (e.g., liposomal surfactants) of the present invention may further comprise palmitic acid, in various preferred embodiments. In one embodiment, the phospholipid comprises about 50-90 weight percent and the palmitic acid comprises the remaining 10-50 weight percent of
20 the lipid portion of the surfactant. As in other preferred embodiments, the phospholipid may be selected from the group consisting of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dipalmitoylphosphatidylcholine, DPPC); phosphatidyl glycerol (PG); and an admixture of DPPC and PG. If an admixture of DPPC
25 and PG is selected, it is preferable that DPPC and PG be present in a weight ratio of about 3:1.

For example, in one embodiment of the present invention, a surfactant composition of the present invention comprises, in each ml of composition, 0.80 mg KL₄ peptide, 19.95 mg DPPC, 6.65
30 mg POPG, and 3.99 mg PA. In various embodiments, the surfactant is prepared aseptically and is supplied in vials containing a sufficient volume to deliver either 2 ml or 5 ml of the

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suspension. Thus, in one exemplary formulation, a preparation having a phospholipid concentration of about 26.6 mg/ml administered at a dosage volume of about 5.0 ml/kg would result in a dose of about 133 mg/kg. Similarly, an exemplary
5 preparation having a phospholipid concentration of about 35 mg/ml administered at a dosage volume of about 5.7 ml/kg would result in a dose of about 200 mg/kg.

One preferred final surfactant composition comprises a sterile liposome suspension containing surfactant polypeptide
10 (or other surfactant molecules according to the present invention). By way of illustration, a drug product/surfactant composition containing KL₄ peptide is described as exemplary.

Peptide is preferably combined with lipids and free fatty acid in an organic solvent system which is then removed by
15 evaporation and vacuum. The dried lipid/peptide mixture is rehydrated in an aqueous buffer system, allowing liposomes to form. While in the organic solvents, the drug components are sterile-filtered and all subsequent processing is performed aseptically.

20 One exemplary composition comprises surfactant peptide and a lipid component. In one embodiment, the lipid component comprises DPPC and/or POPG. In other preferred compositions, the composition also comprises palmitic acid (PA).

For example, a surfactant composition including KL₄ peptide
25 may be prepared from an admixture of DPPC and POPG in a 3:1 ratio by weight with palmitic acid (PA), 15% by weight compared with the phospholipids, in an organic solvent. KL₄ peptide is prepared in the surfactant dispersion as 3% by weight of the phospholipid concentration. Organic solvents were removed from
30 the lipid/peptide mixture by evaporation under nitrogen and vacuum. A Tris buffer solution was added to form liposomes of the peptide-containing surfactant.

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A Tham buffer system may also be included in a surfactant composition of the present invention. (Tham is a buffering agent also known as Tris, tromethamine, and tris(hydroxymethyl)aminomethane.) In various preferred
5 embodiments, the compositions have a pH range of about 6.5 - 8.0.

Thus, in one preferred embodiment, a surfactant composition of the present invention comprises about 0.80 mg peptide, 19.95 mg DPPC, 6.65 mg POPG, 3.99 mg PA, and 1 ml Tham buffer system,
10 per ml of the composition. In another preferred embodiment, a surfactant composition of the present invention includes the following components per ml of Tham buffer of physiologic pH and osmolality: Peptide, 1.05 mg; DPPC, 26.25 mg; POPG, 8.75 mg; and PA, 5.25 mg. Surfactant compositions are preferably
15 prepared aseptically and are supplied as sterile, non-pyrogenic solutions in vials containing sufficient volume to deliver either 2 ml or 6 ml of the suspension.

A wide variety of surfactant molecules, proteins, and polypeptides which are preferred for use according to the
20 disclosed methods are described above and in the sections that follow. Other preferred components of surfactant compositions used as disclosed herein include a variety of phospholipids and palmitic acid, as further described herein.

For example, currently there are a variety of known
25 surfactants described that have been used in related methods. These surfactants are all suitable for use in the present invention according to the discovery that dilute surfactant lavages are beneficial. These surfactants include natural surfactants derived from aqueous lavages of lungs of mammals,
30 including but not limited to bovine, porcine or ovine species, such as BLES, Infasurf or CLSE (Calf Lung Surfactant, Forest Products), Alveofact (Thomae, Germany); surfactant material

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extracted from animal lungs by, but not limited to, organic solvents, such as Surfactant TA (Tokyo Tanabe, Japan), Survanta (Beractant, Abbott Laboratories, Abbott Park, IL), Curosurf (Chiesi Farmaceutici, Parma, Italy).

- 5 In addition, surfactants can comprise various phospholipid or fatty acid molecules such palmitic acid or other factors that induce rapid spreading of the surfactant, either combined with or free of contents of supplemental peptides or proteins. Surfactants may comprise phospholipids, with or without
- 10 detergents, excluding peptides or proteins, such as Exosurf (colfosceril palmitate, cetyl alcohol and tyloxapol; Burroughs-Wellcome, Research Triangle Park, NC), ALEC (Artificial Lung Expanding Compound, Britannia, Ltd.), phospholipid blends, such as DPPC (dipalmitoylphosphatidylcholine) plus
- 15 DOPE(dioleoylphosphatidylethanolamine) and cholesterol, i.e., DOPE-DPPC-cholesterol, (The Liposome Company, Princeton, NJ).

Surfactants can comprise mixtures of phospholipids, spreading agents and proteins or peptides. The phospholipids can be phosphatidyl choline (e.g., DPPC) or phosphatidylglycerol

20 (e.g., POPG) and the like. The spreading agents increase the rate of spreading along an air-water interface and can include palmitic acid, cholesterol, detergents and the like. The proteins and peptides can be any of those described herein or which otherwise augment surfactant activity of phospholipids,

25 and can be isolated from natural sources, synthesized chemically or produced by recombinant DNA methodologies, such as SP-C.

Details regarding the composition and methods of preparation of these and other surfactants can be found in the following U.S. patents: 4,603,124, 5,013,720, 5,024,995,

30 5,171,737, 5,185,154, 5,238,920, 5,302,581, 5,547,937, 5,552,161, and 5,614,216, the disclosures of which are hereby incorporated by reference.

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A surfactant of the present invention is administered, as appropriate to the dosage form, by endotracheal tube, by bronchoscope, by cannula, by aerosol administration, or by nebulization of the suspension or dust into the inspired gas.

5 Amounts of PS between about 1.0 and about 500 mg/kg, and preferably about 50 mg to about 500 mg/kg, and typically a dose of about 50 mg/kg, 100 mg/kg, 133 mg/kg, or 200 mg/kg, measured in terms of total phospholipid content, are administered in one dose. For use in newly born infants, one or two administrations
10 are generally sufficient. For adults, sufficient reconstituted surfactant complex is preferably administered to produce a PO_2 within the normal range (see, e.g., Hallman et al, J. Clinical Investigation, 70:673-682, 1982). It must be appreciated that the treatment regimen may vary from individual to individual,
15 depending on the severity of the RDS, the symptoms present, and other relevant variables; thus, single or multiple doses may be administered to an individual.

As disclosed herein, the invention contemplates the use of both concentrated and dilute surfactant compositions, depending
20 upon the particular use, as described further herein. Concentrated surfactant compositions are typically used for "bolus" type administrations, whereas dilute surfactant compositions are typically used for "lavage" type administrations.

25 Typically, a concentrated surfactant has from 20 to 200 milligrams (mg) of active surfactant compound per milliliter (ml), more preferably about 25 to 100 mg/ml. A typical dilute surfactant has active surfactant compound at a concentration of from about 0.1 to 20 mg/ml, and more preferably about 0.5 to 10
30 mg/ml.

Polypeptides suitable for preparing surfactants in accordance with the present invention are further described in

Section D immediately following.

D. Proteins and Polypeptides

A protein or polypeptide of the present invention
5 (subject protein or polypeptide) is characterized by its amino
acid residue sequence and novel functional properties. A
subject protein or polypeptide when admixed with a
pharmaceutically acceptable phospholipid forms a pulmonary
surfactant having a surfactant activity greater than the
10 surfactant activity of the phospholipid alone. For example, a
protein or polypeptide having a surfactant activity exhibits a
lower ΔP when measured in a surfactant as described in the
Examples.

It is also to be understood that molecules comprising 60 or
15 more amino acid residues -- i.e. protein molecules -- may be
useful in surfactant compositions according to the present
invention. While the present disclosure focuses primarily upon
polypeptide molecules and molecules including amino acid
residues, analogs, and/or other organic molecules, proteins
20 having alternating hydrophobic and hydrophilic amino acid
residue regions and proteins having surfactant ability as
described herein are also contemplated by -- and encompassed by
-- the present disclosures.

Molecules demonstrating surfactant activity which comprise
25 10 or fewer amino acid residues are also contemplated by the
present invention. For example, a molecule comprising five
amino acid residues linked to five amino acid derivatives or
analogs may be useful as disclosed herein, particularly if it
has alternating hydrophobic and hydrophilic amino acid residue
30 regions and has surfactant ability, as defined herein. Thus,
molecules comprising two to 100 amino acid residues having a
configuration that maximizes their interaction with the alveoli

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are contemplated by the present invention. While larger molecules are somewhat more difficult to synthesize, it should be appreciated by those of skill in the relevant art that, as disclosed herein, even molecules containing 60 or more amino acid residues (or their analogs) may be excellent surfactants, provided they possess the disclosed characteristics.

Polypeptides suitable for preparing liposomal surfactants in accordance with the present invention can be synthesized from amino acids by techniques that are known to those skilled in the polypeptide art. An excellent summary of the many techniques available may be found in J.M. Steward and J.D. Young, "Solid Phase Peptide Synthesis", W.H. Freeman Co., San Francisco, 1969, and J. Meienhofer, "Hormonal Proteins and Peptides", Vol. 2, p. 46, Academic Press (New York), 1983 for solid phase peptide synthesis, and E. Schroder and K. Kubke, "The Peptides", Vol. 1, Academic Press (New York), 1965 for classical solution synthesis.

In general, these methods comprise the sequential addition of one or more amino acid residues or suitably protected amino acid residues to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid residue is protected by a suitable, selectively removable protecting group. A different, selectively removable protecting group is utilized for amino acids containing a reactive side group (e.g., lysine).

Using a solid phase synthesis as exemplary, the protected or derivatized amino acid is attached to an inert solid support through its unprotected carboxyl or amino group. The protecting group of the amino or carboxyl group is then selectively removed and the next amino acid in the sequence having the complementary (amino or carboxyl) group suitably protected is admixed and reacted under conditions suitable for forming the amide linkage with the residue already attached to the solid support. The

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protecting group of the amino or carboxyl group is then removed from this newly added amino acid residue, and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining terminal and side group protecting groups (and any solid support) are removed sequentially or concurrently, to afford the final polypeptide. That polypeptide is then washed by dissolving in a lower aliphatic alcohol, and dried. The dried surfactant polypeptide can be further purified by known techniques, if desired. (Various methods of preparing polypeptides of the present invention are also described in the Examples below.)

Preferably, the surfactant polypeptides are polypeptides that include amino acid residue sequences having alternating charged and uncharged amino acid residue regions. Polypeptides including amino acid residue sequences having alternating hydrophobic and hydrophilic amino acid residue regions are also preferred according to the present invention. Particularly preferred surfactant polypeptides within these groupings are further characterized as having at least about 4, more preferably at least about 8, and even more preferably at least about 10, amino acid residues, and are generally not more than about 60 amino acid residues in length.

Preferably, surfactant polypeptides of the present invention are constituted by alternating groupings of charged amino acid residues and uncharged amino acid residues as represented by the formula $[(\text{Charged})_a(\text{Uncharged})_b]_c(\text{Charged})_d$, wherein a has an average value of about 1 to about 5; b has an average value of about 3 to about 20; c is 1 to 10; and d is 0 to 3. Organic surfactant molecules not comprised solely of amino acid residues alone preferably have a similar structure constituted by alternating groupings of charged and uncharged

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(or hydrophilic/hydrophobic) constituent molecules.

In one preferred embodiment, surfactant polypeptides include a sequence having alternating groupings of amino acid residues as represented by the formula $(Z_a J_b)_c Z_d$, wherein Z is an amino acid residue independently selected from the group consisting of R, D, E, and K; J is an α -aminoaliphatic carboxylic acid; a has an average value of about 1 to about 5; b has an average value of about 3 to about 20; c is 1 to 10; and d is 0 to 3.

10 In another embodiment, preferred polypeptides of the present invention have alternating groupings of amino acids residue regions as represented by the formula $(B_a U_b)_c B_d$, wherein B is an amino acid residue independently selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-
15 hydroxyproline; and U is an amino acid residue independently selected from the group consisting of V, I, L, C, Y, and F. In one preferred variation, B is an amino acid derived from collagen and is preferably selected from the group consisting of 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline; a has
20 an average value of about 1 to about 5; b has an average value of about 3 to about 20; c is 1 to 10; and d is 0 to 3.

In still another preferred embodiment, surfactant polypeptides of the present invention include a sequence having alternating groupings of amino acid residues as represented by
25 the formula $(B_a J_b)_c B_d$, wherein B is an amino acid residue independently selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline; and J is an α -aminoaliphatic carboxylic acid; a has an average value of about 1 to about 5; b has an average value of about 3 to about
30 20; c is 1 to 10; and d is 0 to 3.

In various embodiments including "J" in the relevant formula, J is an α -aminoaliphatic carboxylic acid having four to

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six carbons, inclusive. In other preferred variations, J is an α -aminoaliphatic carboxylic acid having six or more carbons, inclusive. In yet other variations, J is preferably selected from the group consisting of α -aminobutanoic acid, α -aminopentanoic acid, α -amino-2-methylpropanoic acid, and α -aminohexanoic acid.

Another preferred embodiment discloses surfactant polypeptides including a sequence having alternating groupings of amino acid residues as represented by the formula $(Z_a U_b)_c Z_d$, wherein Z is an amino acid residue independently selected from the group consisting of R, D, E, and K; and U is an amino acid residue independently selected from the group consisting of V, I, L, C, Y and F; from the group consisting of V, I, L, C and F; or from the group consisting of L and C; a has an average value of about 1 to about 5; b has an average value of about 3 to about 20; c is 1 to 10; and d is 0 to 3.

In the foregoing formulae, Z and U, Z and J, B and U, and B and J are amino acid residues that, at each occurrence, are independently selected. In addition, in each of the aforementioned formulae, a generally has an average value of about 1 to about 5; b generally has an average value of about 3 to about 20; c is 1 to 10; and d is 0 to 3.

In one variation of the foregoing embodiments, Z and B are charged amino acid residues. In other preferred embodiments, Z and B are hydrophilic or positively charged amino acid residues. In one variation, Z is preferably selected from the group consisting of R, D, E and K. In a related embodiment, Z is preferably selected from the group consisting of R and K. In yet another preferred embodiment, B is selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline. In one preferred embodiment, B is H. In another preferred embodiment, B is a collagen constituent amino

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acid residue and is selected from the group consisting of 5-hydroxylysine, (δ -hydroxylysine), 4-hydroxyproline, and 3-hydroxyproline.

In various disclosed embodiments, U and J are, preferably, 5 uncharged amino acid residues. In another preferred embodiment, U and J are hydrophobic amino acid residues. In one embodiment, U is preferably selected from the group consisting of V, I, L, C, Y, and F. In another preferred embodiment, U is selected from the group consisting of V, I, L, C, and F. In yet another 10 preferred embodiment, U is selected from the group consisting of L and C. In various preferred embodiments, U is L.

Similarly, in various embodiments, B is an amino acid preferably selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline. 15 Alternatively, B may be selected from the group consisting of collagen-derived amino acids, which includes 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline.

In another embodiment of the present invention, charged and uncharged amino acids are selected from groups of modified amino 20 acids. For example, in one preferred embodiment, a charged amino acid is selected from the group consisting of citrulline, homoarginine, or ornithine, to name a few examples. Similarly, in various preferred embodiments, the uncharged amino acid is selected from the group consisting of α -aminobutanoic acid, α -aminopentanoic acid, α -amino-2-methylpropanoic acid, and α -aminohexanoic acid. 25

In preferred embodiments of the present invention, items "a", "b", "c" and "d" are numbers which indicate the number of charged or uncharged residues (or hydrophilic or hydrophobic 30 residues). In various embodiments, "a" has an average value of about 1 to about 5, preferably about 1 to about 3, more preferably about 1 to about 2, and even more preferably, 1.

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In various embodiments, "b" has an average value of about 3 to about 20, preferably about 3 to about 12, more preferably about 3 to about 10, even more preferably in the range of about 4-8. In one preferred embodiment, "b" is about 4.

5 In various embodiments, "c" is 1 to 10, preferably 2 to 10, more preferably in the range of 3-8 or 4-8, and even more preferably 3 to 6. In one preferred embodiment, "c" is about 4.

In various embodiments, "d" is 0 to 3 or 1 to 3. In one preferred embodiment, "d" is 0 to 2 or 1 to 2; in another
10 preferred embodiment, "d" is 1.

By stating that an amino acid residue -- e.g., a residue represented by Z or U -- is independently selected, it is meant that at each occurrence, a residue from the specified group is selected. That is, when "a" is 2, for example, each of the
15 hydrophilic residues represented by Z will be independently selected and thus can include RR, RD, RE, RK, DR, DD, DE, DK, etc. By stating that "a" and "b" have average values, it is meant that although the number of residues within the repeating sequence (e.g., $Z_a U_b$) can vary somewhat within the peptide
20 sequence, the average values of "a" and "b" would be about 1 to about 5 and about 3 to about 20, respectively.

For example, using the formula $(Z_a U_b)_c Z_d$ for the peptide designated "KL8" in Table 1 below, the formula can be rewritten as $K_1 L_8 K_1 L_8 K_1 L_2$, wherein the average value of "b" is six
25 [i.e., $(8+8+2)/3 = 6$], c is three and d is zero.

Exemplary preferred polypeptides of the above formula are shown in Table 1 below:

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Table 1

	<u>Designation</u> ¹	<u>SEO ID NO</u>	<u>Amino Acid Residue Sequence</u>
	KL4	1	KL L L L K L L L L K L L L L K L L L L K
5	KL8	2	KL L L L L L L L L K L L L L L L L L L K L L
	KL7	3	KK L L L L L L L L K K L L L L L L L L K K L
	DL4	4	DL L L L D L L L L D L L L L D L L L L D
	RL4	5	RL L L L R L L L L R L L L L R L L L L R
	RL8	6	RL L L L L L L L L R L L L L L L L L L R L L
10	RL7	7	RR L L L L L L L L R R L L L L L L L L R R L
	RCL1	8	RL L L L C L L L R L L L L C L L L R
	RCL2	9	RL L L L C L L L R L L L L C L L L R L L
	RCL3	10	RL L L L C L L L R L L L L C L L L R L L L L C L L L R
15	HL4	13	HL L L L H L L L L H L L L L H L L L L H

¹ The designation is an abbreviation for the indicated amino acid residue sequence.

Also suitable are composite polypeptides of about 4 to 60 amino acid residues having a configuration that maximizes their interaction with the alveoli. A composite polypeptide consists essentially of an amino terminal sequence and a carboxy terminal sequence. The amino terminal sequence has an amino acid sequence of a hydrophobic region polypeptide or a hydrophobic peptide of this invention, preferably hydrophobic polypeptide, as defined in the above formula. The carboxy terminal sequence has the amino acid residue sequence of a subject carboxy terminal peptide.

Proteins and polypeptides derived from or having characteristics similar to those of natural Surfactant Protein (SP) are useful in the present methods. As noted, SP isolated from any mammalian species may be utilized, although bovine, porcine and human surfactants are particularly preferred.

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Natural surfactant proteins include SP-A, SP-B, SP-C or SP-D, or fragments thereof, alone or in combination with lipids. A preferred fragment is the amino-terminal residues 1-25 of SP-B.

A related peptide is the WMAP-10 peptide (Marion Merrell
5 Dow Research Institute) having the sequence succinyl-Leu-Leu-Glu-Lys-Leu-Leu-Gln-Trp-Lys-amide. Alternative peptides are polymers of lysine, arginine or histidine that induce a lowering of surface tension in admixtures of phospholipids as described herein.

10 In addition, human SP18 (SP-B) surfactant protein may be utilized as described herein. See, e.g., U.S. Patent Nos. 5,407,914; 5,260,273; and 5,164,369, the disclosures of which are incorporated by reference herein.

Thus, in one embodiment, a surfactant molecule of the
15 present invention comprises a polypeptide. In one variation, a surfactant polypeptide comprises about 4, more preferably about 10, amino acid residues. In various embodiments, a surfactant polypeptide preferably comprises 60 or fewer amino acid residues, more usually fewer than about 35, and even more
20 preferably, fewer than about 25 amino acid residues. In various preferred embodiments, subject polypeptides correspond to the sequence of SP18 monomer -- e.g., a single group of contiguous residues in the linear sequence of SP18. In other embodiments, subject polypeptides preferably have alternating charged and
25 uncharged amino acid residue regions or have alternating hydrophobic and hydrophilic amino acid residue regions.

Polypeptides of the present invention may also be subject to various changes, such as insertions, deletions and substitutions, either conservative or non-conservative, where
30 such changes provide for certain advantages in their use. Conservative substitutions are those in which one amino acid residue is replaced by another, biologically similar residue.

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Examples of conservative substitutions include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another such as between arginine and lysine, between
5 glutamic and aspartic acids or between glutamine and asparagine and the like. The term "conservative substitution" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that such a polypeptide also displays the requisite binding activity.

10 Additional residues may be added at either terminus of a polypeptide of the present invention, such as for the purpose of providing a "linker" by which such a polypeptide can be conveniently affixed to a label or solid matrix, or carrier. Labels, solid matrices and carriers that can be used with the
15 polypeptides of this invention are known in the art; some examples are also described herein.

Amino acid residue linkers are usually at least one residue and can be 40 or more residues, more often 1 to 10 residues. Typical amino acid residues used for linking are tyrosine,
20 cysteine, lysine, glutamic and aspartic acid, or the like. In addition, a polypeptide sequence of this invention can differ from the natural sequence by the sequence being modified by terminal-NH₂ acylation, e.g., acetylation, or thioglycolic acid amidation, terminal-carboxlyamidation, e.g., ammonia,
25 methylamine, etc.

In another embodiment, a polypeptide of this invention has amino acid residue sequence that has a composite hydrophobicity of less than zero, preferably less than or equal to -1, more preferably less than or equal to -2. Determination of the
30 composite hydrophobicity value for a peptide is described in detail in Example 3. These hydrophobic polypeptides perform the function of the hydrophobic region of SP18. Thus, in one

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preferred embodiment, the amino acid sequence mimics the pattern of charged and uncharged -- or hydrophobic and hydrophilic -- residues of SP18.

It should be understood, however, that polypeptides and
5 other surfactant molecules of the present invention are not limited to molecules having sequences like that of native SP18. On the contrary, some of the most preferred surfactant molecules of the present invention have little resemblance to SP18 with respect to a specific amino acid residue sequence, except that
10 they have similar surfactant activity and alternating charged/uncharged (or hydrophobic/hydrophilic) residue sequences.

One disclosed embodiment of the present invention comprises a peptide-containing preparation, the 21-residue peptide being a
15 mimic of human SP-B consisting of repeated units of four hydrophobic leucine (L) residues, bounded by basic polar lysine (K) residues. This exemplary peptide, which is abbreviated herein as "KL₄," has the following amino acid residue sequence: KLLLLKLLLLKLLLLKLLLLK (SEQ ID NO 1).

20 Combined with the phospholipids dipalmitoyl phosphatidylcholine and palmitoyl-, oleoylphosphatidyl glycerol (3:1) and palmitic acid, the phospholipid-peptide aqueous dispersion has been named "KL₄-Surfactant," and it is generally referred to herein in that manner. The efficacy of KL₄-
25 Surfactant in various experimental and clinical studies has been previously reported. See, e.g., Cochrane et al, Science, 254:566-568 (1991); Vincent et al., Biochemistry, 30:8395-8401 (1991); Cochrane et al., Am J Resp & Crit Care Med, 152:404-410 (1996); and Revak et al., Ped. Res., 39:715-724 (1996).

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E. Amino Acids, Natural Metabolites, Derivatives,
Designed Analogs, and Other Organic Molecules

Surfactant molecules of the present invention also include organic molecules having surfactant activity, as defined
5 above and as further described herein. While polypeptides and proteins are often described as exemplary, it should be understood that surfactant molecules of the present invention are not limited to those having either conventional amino acid side chains or a polyamide backbone structure.

10 As noted previously, the present invention contemplates a variety of surfactant molecules, including proteins, polypeptides, and molecules including amino acid residues, as well as a variety of surfactant compositions. While one tends to think of the "common" natural amino acids (i.e., those listed
15 in the "Table of Correspondence" in Section A above) as being preferred for use in biological compositions, it is also true that a wide variety of other molecules, including uncommon but naturally occurring amino acids, metabolites and catabolites of natural amino acids, substituted amino acids, and amino acid
20 analogs, as well as amino acids in the "D" configuration, are useful in molecules and compositions of the present invention. In addition, "designed" amino acid derivatives, analogs and mimics are also useful in various compounds, compositions and methods of the present invention, as well as polymers including
25 backbone structures composed of non-amide linkages.

For example, in addition to the L-amino acids listed in the "Table of Correspondence" in Section A above, amino acid metabolites such as homoarginine, citrulline, ornithine, and α -aminobutanoic acid are also useful in molecules and compositions
30 of the present invention. Thus, in the various formulas described above, "Charged", Z, or B may comprise homoarginine, citrulline, or ornithine, as well as a variety of other

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molecules as identified herein. Similarly, J may comprise α -aminobutanoic acid (also known as α -aminobutyric acid), α -aminopentanoic acid, α -aminohexanoic acid, and a variety of other molecules identified herein.

5 Further, substituted amino acids which are not generally derived from proteins, but which are known in nature, are useful as disclosed herein, include the following examples: L-canavanine; 1-methyl-L-histidine; 3-methyl-L-histidine; 2-methyl-L-histidine; α,ϵ -diaminopimelic acid (L form, *meso* form, or
10 both); sarcosine; L-ornithine betaine; betaine of histidine (herzynine); L-citrulline; L-phosphoarginine; D-octopine; O-carbamyl-D-serine; γ -aminobutanoic acid; and β -lysine. D-amino acids and D-amino acid analogs, including the following, are also useful in proteins, peptides and compositions of the
15 present invention: D-alanine, D-serine, D-valine, D-leucine, D-isoleucine, D-alloisoleucine, D-phenylalanine, D-glutamic acid, D-proline, and D-allohydroxyproline, to name some examples. The foregoing may also be used in surfactant molecules according to the present invention; particularly preferred for use
20 accordingly are those corresponding to the formula $\{(\text{Charged})_a(\text{Uncharged})_b\}_c(\text{Charged})_d$.

The present invention also discloses that an extensive variety of amino acids, including metabolites and catabolites thereof, may be incorporated into molecules which display a
25 surfactant activity. For example, molecules such as ornithine, homoarginine, citrulline, and α -aminobutanoic acid are useful components of molecules displaying surfactant activity as described herein. Surfactant molecules according to the present invention may also comprise longer straight-chain molecules; α -
30 aminopentanoic acid and α -aminohexanoic acid are two additional examples of such useful molecules.

It should also be appreciated that the present invention

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encompasses a wide variety of modified amino acids, including analogs, metabolites, catabolites, and derivatives, irrespective of the time or location at which modification occurs. In essence, one may place modified amino acids into three

5 categories: (1) catabolites and metabolites of amino acids; (2) modified amino acids generated via posttranslational modification (e.g., modification of side chains); and (3) modifications made to amino acids via non-metabolic or non-

10 or derivatives in the laboratory).

The present invention also contemplates that one may readily design side chains of the amino acids of residue units that include longer or shortened side chains by adding or subtracting methylene groups in either linear, branched chain,

15 or hydrocarbon or heterocyclic ring arrangements. The linear and branched chain structures may also contain non-carbon atoms such as S, O, or N. Fatty acids may also be useful constituents of surfactant molecules herein. The designed side chains may terminate with (R') or without (R) charged or polar group

20 appendages.

In addition, analogs, including molecules resulting from the use of different linkers, are also useful as disclosed herein. Molecules with side chains linked together via linkages other than the amide linkage -- e.g., molecules containing amino

25 acid side chains or other side chains (R- or R'-) wherein the components are linked via carboxy- or phospho-esters, ethylene, methylene, ketone or ether linkages, to name a few examples -- are also useful as disclosed herein. In essence, any amino acid side chain, R or R' group-containing molecule may be useful as

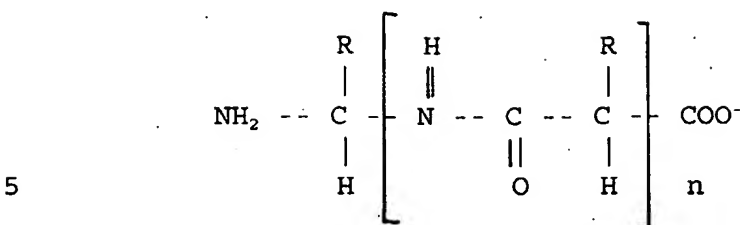
30 disclosed herein, as long as the molecule includes alternating hydrophilic and hydrophobic residues (i.e., component molecules) and displays surfactant activity as described herein.

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The present invention also contemplates molecules comprising peptide dimers joined by an appropriate linker -- e.g., peptide dimers linked by cystine molecules. (As those of skill in the art are aware, two cysteine molecules may be linked together by a disulfide bridge formed by oxidation of their thiol groups.) Such linkers or bridges may thus cross-link different polypeptide chains, dimers, trimers, and the like. Other useful linkers which may be used to connect peptide dimers and/or other peptide multimers include those listed above -- e.g., carboxy- or phospho-ester, ethylene, methylene, ketone or ether linkages, to name a few examples.

While it is appreciated that many useful polypeptides disclosed herein -- e.g., the KL4 polypeptide (SEQ ID NO 1) -- comprise naturally-occurring amino acids in the "L" form which are joined via peptide linkages, it should also be understood that molecules including amino acid side chain analogs, non-amide linkages (e.g., differing backbones) may also display a significant surfactant activity and may possess other advantages, as well. For example, if it is desirable to construct a molecule (e.g., for use in a surfactant composition) that is not readily degraded, one may wish to synthesize a polypeptide molecule comprising a series of D-amino acids. Molecules comprising a series of amino acids linked via a "retro" backbone -- i.e., a molecule that has internal amide bonds constructed in the reverse direction of carboxyl terminus to amino terminus -- are also more difficult to degrade and may thus be useful in various applications, as described herein. For example, the following illustrates an exemplary molecule with a "retro" bond in the backbone:

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In another variation, one may wish to construct a molecule that adopts a more "rigid" conformation; one means of accomplishing this would be to add methyl or other groups to the α carbon atom of the amino acids.

As noted above, other groups besides a CH_3 group may be added to the α carbon atom -- that is, surfactant molecules of the present invention are not limited to those incorporating a CH_3 at the α carbon alone. For example, any of the side chains and molecules described above may be substituted for the indicated CH_3 group at the α carbon component.

As used herein, the terms "analogs" and "derivatives" of polypeptides and amino acid residues are intended to encompass metabolites and catabolites of amino acids, as well as molecules which include linkages, backbones, side-chains or side-groups which differ from those ordinarily found in what are termed "naturally-occurring" L-form amino acids. (The terms "analog" and "derivative" may also conveniently be used interchangeably herein.) Thus, D-amino acids, molecules which mimic amino acids and amino acids with "designed" side chains (i.e., that can substitute for one or more amino acids in a molecule having surfactant activity) are also encompassed by the terms "analogs" and "derivatives" herein.

A wide assortment of useful surfactant molecules, including amino acids having one or more extended or substituted R or R' groups, is also contemplated by the present invention. Again, one of skill in the art should appreciate from the disclosures that one may make a variety of modifications to individual amino

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acids, to the linkages, and/or to the chain itself -- which modifications will produce molecules falling within the scope of the present invention -- as long as the resulting molecule possesses surfactant activity as described herein.

5

F. Therapeutic Methods

The present application also discloses a variety of therapeutic methods that are useful in conjunction with various novel compounds and compositions disclosed herein. While the
10 use of KL₄-surfactant is described herein as exemplary, it should be understood that the other compounds and compositions disclosed herein -- as well as compounds and compositions having surfactant activity and known to those of skill in the art -- are also useful according to the described methods.

15 The present invention also discloses preferred methods of treating respiratory distress syndrome in patients of any age, including neonates and adults. One such method comprises administering to a patient in need of such treatment a therapeutically effective amount of a surfactant composition --
20 preferably, a liposomal surfactant composition -- prepared from a polypeptide (or other surfactant molecule) of the present invention and a pharmaceutically acceptable phospholipid, wherein the polypeptide is combined with the phospholipid in an amount sufficient to increase the surfactant activity of the
25 composition above that of the phospholipid. The present invention also discloses a method of treating respiratory distress syndrome wherein the polypeptide is constituted by about 10-60 amino acid residues and alternating groupings of charged amino acid residues and uncharged amino acid residues as
30 represented by the formula $[(\text{Charged})_a(\text{Uncharged})_b]_c(\text{Charged})_d$, wherein a has an average value of about 1 to about 5; b has an average value of about 3 to about 20; c is 1 to 10; and d is 0

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to 3. In various preferred embodiments, such a polypeptide, when admixed with a pharmaceutically acceptable phospholipid, forms a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

5 As illustrated in the various Examples set forth below, a variety of methods for administering the surfactant compounds and compositions of the present invention are available. Depending on the needs of any individual needing treatment -- e.g., an infant or adult with respiratory distress syndrome --
10 different treatment methods may be appropriate.

Thus, in instances in which an infant has aspirated meconium, particular treatment modalities may be recommended. In one such therapeutic method, lavage of the patient's lungs with a surfactant composition of the present invention is
15 performed. A single lavage with surfactant may be all that is required; alternatively, multiple surfactant lavages may be appropriate. Moreover, a saline lavage followed by one or more surfactant lavages may be an appropriate treatment -- albeit it will be shown below that dilute surfactant lavage tends to
20 produce better results than a combination of saline and surfactant lavage.

Lavage procedures using surfactant are performed essentially as follows. KL₄-surfactant or another surfactant (e.g. one of the present invention) is preferably administered
25 using tools typically used in saline lavage procedures, which include various flexible tube-like apparatus such as endotracheal tubes, cannulas and catheters. Thus, for example, an endotracheal tube apparatus which includes a cannula that may be inserted through the tube -- e.g. for suctioning purposes --
30 is appropriate for use according to the disclosed methods. Preferably, any apparatus appropriately used to safely and efficaciously deliver and remove lavage fluids to and from the

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lung, respectively, is contemplated for use herein.

Exemplary devices for pulmonary lavage are ventilator devices equipped for bronchoalveolar lavage (BAL), which must include a means for applying a positive end-expiratory pressure (PEEP) to the lung, a means for instilling liquids into the lung and a means for removing pulmonary fluids from the lung using negative pressure suction.

Representative devices are described in U.S. Patent Nos. 4,895,719, 5,207,220, 5,299,566 and 5,309,903, the disclosures of which are hereby incorporated by reference.

As shown herein, particularly advantageous results were obtained by practicing a method of pulmonary lavage using dilute surfactant that produced sustained recovery of arterial oxygen (PaO_2), normal lung compliance and diminished inflammation following pulmonary injury by meconium aspiration or by partial loss of intrinsic surfactant, such as is demonstrated herein in the model using instillation of bacterial LPS. These methods are believed useful for use in treating any of a variety of pulmonary conditions in which there is respiratory distress, particularly acute respiratory distress syndrome (ARDS).

Conditions in which respiratory stress may be present include, but are not limited to, meconium aspiration in newborn infants, pulmonary inflammation, pulmonary infection. Respiratory distress can be associated with a variety of conditions, including sepsis, pulmonary trauma, accumulation of pulmonary exudate, pancreatitis, aspiration of gastric contents, heated gas inhalation, smoke or noxious gas inhalation, acute hypoxemia, fetal circulation, congenital diaphragmatic hernia, pneumonia, inflammation arising from infection or multiple transfusions, and the like.

As shown herein, the present dilute surfactant lavage methods remove mediators of inflammation and simultaneously

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preserve and/or restore pulmonary function, thereby providing effective therapy.

The application of the pulmonary lavage provides several beneficial features. The washing effect of the lavage removes
5 debris, dead cells, loose inflammatory cells and fluids, and the like, cleaning the alveoli of occluding fluid and materials, and removing typically 30 to 95 % of the pulmonary and lavage fluids, together with any undesirable materials, such as meconium or inflammatory exudates. The dilute surfactant treats
10 the alveolar membranes, improving the compliance of the tissue. The application of specified amounts of ventilator air pressure in the form of positive end-expiratory pressure (PEEP) before, during and after lavage with surfactant expands the lungs to maximize contact in the wash and treatment phase and thereby
15 improve the dynamics of the lavage process, and in particular improves the oxygen tension and gas exchange in the patient during a process that can precariously burden oxygen exchange in the alveoli. Finally, the use of short intervals of tracheo-bronchial suction to remove the pulmonary (lavage) fluids are
20 carefully administered in a manner that does not allow the arterial oxygen saturation to be reduced below acceptable and safe levels.

The pulmonary lavage method can be practiced on any mammal, and is particularly suited for humans, including adults,
25 juveniles and infants, both newborn infants and babies experiencing respiratory distress.

The method for pulmonary lavage of a mammal comprises applying vapor phase (gas) positive end-expiratory pressure (PEEP) with a ventilator means to a lung, lung section or lobe
30 of the mammal. Thereafter, a lavage composition containing dilute surfactant in a pharmaceutically acceptable aqueous medium is instilled into the lung or lung section of the mammal.

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Afterwards, some or all pulmonary fluid, including the lavage composition, present in the lung section is removed by applying short intervals of tracheo-bronchial suction using negative pressure.

5 The PEEP is typically administered at a pressure range of 4 to 20 centimeters (cm) water, although the pressure can vary depending on the patient and the pulmonary condition. For adults, juveniles and infants other than newborns, in which the lungs have toughened, the range is preferably from 6 to 12 cm
10 water, and more preferably about 8-10 cm water. For newborn infants in which the lung sacs are more delicate and more fragile to applied pressure, the PEEP can range from about 4 to 15 cm water, preferably about 6 to 9 cm water, and more preferably about 8 cm water.

15 The administration of gas PEEP is typically applied to the lung prior to instilling dilute surfactant lavage, typically for up to about 30 minutes prior, more preferably about 5 to 30 minutes, in order to stabilize the blood oxygen prior to the procedure. In addition, PEEP is preferably applied continuously
20 throughout the procedure during both the instilling and removing steps. It is to be understood that the combined effect on pressure of applying continuous PEEP and a short interval of suction will result in a brief, transient, drop in net pressure, with a rapid return to the maintained PEEP level when the
25 suction interval is terminated. In addition, PEEP can be applied for a time period after the lavage fluid removal step in order to maintain oxygen tension on the alveoli following the procedure. Preferably, PEEP is maintained for up to about 24 hours after the removing step, preferably up to about 12 hours,
30 and more preferably about 0.5 to 6 hours.

It is also contemplated that the applied gas can contain supplemental oxygen, typically from about 21 to 100 % oxygen,

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preferably about 50 to 100 % oxygen.

The suction phase of the method to remove the lavage and pulmonary fluids is administered in short intervals, i.e, 1 to 120 seconds. A typical suctioning interval is less than 30
5 seconds, preferably less than 20 seconds, and more preferably for about 5 to 20 seconds. A preferred interval is from 2 to 120 seconds, and preferably 5 to 20 seconds. The suction time period is short in order to minimize decreases in and saturated arterial oxygen (SaO_2) that may accompany the suction phase of
10 the lavage procedure.

In one permutation of the suction procedure where there is more than one suction required to remove the pulmonary fluid, it is desirable to pause between short suction intervals rather than to follow one suction interval immediately with another in
15 order to provide the opportunity for the PaO_2 level to recover. A typical pause period is from about 30 seconds to fifteen minutes, preferably about 1-5 minutes.

The suction applied to remove pulmonary fluids is a negative pressure of from about 10 to 150 millimeters (mm)
20 mercury (Hg), preferably about 20 to 120 mm Hg, and more preferably about 60 to 100 mm Hg. A suction catheter or similar suction means is present in the ventilator device, typically as a cannula extending through the ventilator tube of the apparatus and into the bronchus. The cannula tip is typically guided into
25 a segmental bronchus with the aid of the fiber optic observing means, and the instilling and removing are provided through the cannula tip.

In practicing the dilute lavage method, it is understood that the lavage can be administered repeatedly. Thus, the
30 instilling and removing steps are repeated sequentially while applying PEEP as described herein. Typically, instilling and removing (lavage wash cycles) can be repeated in sequence from 2

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to 5 times, although additional repetitions can be conducted if warranted. In addition, the content of the dilute surfactant can be varied over the course of the repeated lavage washes. For example, it is contemplated that a first series of from 1 to 5 3 wash cycles are conducted using dilute surfactant at a concentration of about 0.1 to 10 mg per ml lavage composition, and a second series of from 1 to 5 wash cycles are conducted using dilute surfactant at a concentration of about 10 to 50 mg per ml.

10 Depending on the position of the endotracheal tube apparatus in lung, the lavage composition will bathe a lung lobe, a lung segment or an entire side of lung, this being determined by the position in the bronchial tube where the apparatus terminates. Thus, it is understood that the term 15 "lung" connotes alternatively that a lung lobe, a lung segment, a lung half containing two or three lobes, or a whole lung is being referred to in the context of the method, but adjusted for volume based on weight of the patient.

In instilling a lavage composition, it is also understood 20 that the process can be conducted by a variety of methods, such as by cannula, by bronchoscope, by endotracheal tube and the like. In a preferred method, the instilling is typically monitored visually by a means for observing the lung at the apparatus tube terminus, typically by use of a fiber optic 25 bronchoscope and illuminating means for visual display of the bronchial tube and distal lung lobe(s). Thus, although estimates of the appropriate lavage composition volume are stated, it is understood that in practice, the instilled volume may depend on the judgement of the practitioner during the 30 instilling process, aided by the observing means.

The pulmonary lavage process is typically conducted on as many lungs, both left and right, and involved lung lobes, as

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needed depending on the extent of the condition of the lungs. Typically the procedure is conducted sequentially on 30 to 100 % of the bronchial segments of the left and right lungs.

The bronchoscope or endotracheal tube may be fitted with a
5 fixed or expanding collar designed to fit the inner diameter of a bronchial passage, and thereby secure a fit that can withstand the pressure ranges for practicing the method. This feature is particularly desirable insofar as it allows a section of the lung to be lavaged while the remaining lung portions can
10 respire, thereby minimizing the trauma of the procedure to gas exchange in the patient.

KL₄-Surfactant solution or other novel surfactant solutions according to the present invention may be administered via lavage in a formulation appropriate for this procedure. While
15 we have found that a formulation of surfactant comprising about 10-20 ml/kg is useful in the treatment of respiratory distress syndrome, formulations for lavage therapy tend to be more dilute, to facilitate efficient delivery and removal via endotracheal tube.

20 Thus, a "dilute surfactant" when used in the context of a lavage composition indicates that the lavage composition contains one or more substances which provide surfactant activity to the composition as defined herein in an amount sufficient to provide the surfactant activity but present in an
25 amount such that the composition has a liquid viscosity amenable to lavage.

Thus, a surfactant-containing composition useful for administration to a subject (or patient) via lavage is preferably diluted to a concentration of about up to about 50
30 mg/ml so long as the viscosity is such that the composition is amenable to suction removal in less than 30 seconds following instillation. Dosages in the range of about 0.1 - 50 mg/ml are

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typically contemplated for use herein. In addition, the administration of higher dosages may be appropriate in various instances -- e.g., when the subject is not fully responsive to lower dosages, or where the formulation lowers viscosity while
5 allowing for increased concentrations of surfactant activity-containing substances.

In general, quantities of surfactant of about 4 to 60 ml per kg of the subject's (or patient's) body weight are given during each administration, typically divided equally between
10 right lung and left lung or divided among lung sections. Depending on the needs of the individual patient -- which may readily be determined by the physician or other individual of skill in the relevant art who is administering the treatment -- greater or lesser quantities of surfactant may be delivered
15 during each administration. Quantities comprising about 8-30 ml/kg are preferred, with quantities comprising about 10-25 ml/kg being somewhat more preferred. Thus, lavage composition is typically instilled in a volume of about 4 to 60 ml per kilogram (kg), preferably about 8 to 30 ml per kg, and more
20 preferably about 16-25 ml per kg.

In describing the amount of surfactant present in a lavage composition, the weight refers to an amount measured as phospholipid phosphate per total volume of lavage composition, unless otherwise specified.

25 The amount of surfactant administered via lavage may also be described "per lung" in a particular patient. Thus, an effective amount of surfactant for lavage purposes may comprise about 200-800 ml/lung for a 70 kg adult, preferably about 400 ml/lung, and about 30-60 ml/lung for a 3 kg infant, preferably
30 about 50 ml/lung. As before, depending on the maturity and size of the individual receiving treatment, the amount of surfactant administered -- as well as the dosage -- may be adjusted as

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appropriate.

A subject may receive one or more lavages, depending on the severity of the individual's condition and depending on the response of the subject to the first lavage. The dosages and
5 amounts of surfactant administered may likewise vary in subsequent lavages. For example, if a subject receives a typical dose during the first lavage, subsequent lavages may be administered using the same dosage, a lesser dosage, or a higher dosage, depending on the needs and response of the subject.

10 Similarly, the amounts of surfactant administered during each lavage may vary -- or may remain constant -- depending on the needs of the individual patient. In appropriate circumstances, the first or subsequent lavage may be followed by a lavage administering a higher dose -- e.g., up to 10-50 mg/ml.
15 For example, a subject may receive 1-3 lavages with surfactant at a concentration of 0.1 - 10 mg/ml followed by 1-5 lavages with surfactant at a concentration of 10-50 mg/ml.

As noted previously, the dosage to be administered varies with the size and maturity of the subject, as well as with the
20 severity of the subject's condition. Those of skill in the relevant art will be readily able to determine these factors and to adjust the dosage administered via lavage, as taught herein.

Bolus administration of surfactant may also be appropriate. Thus, for example, a bolus of 10-300 mg/kg surfactant at 15-100
25 mg/ml may be administered prior to or subsequent to one or more lavage treatments.

The type of treatment, dosage and amount utilized will understandably vary depending on the nature and seriousness of an individual subject's condition. Thus, for example, if a
30 subject is an infant suffering from meconium aspiration, a treatment regimen comprising one or more surfactant lavages will likely be administered. Bolus administration of surfactant may

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follow the lavage(s) as well.

As noted previously, one aspect of the present invention was the removal of meconium or inflammatory exudate from the airways via lavage with dilute surfactant, in order to improve pulmonary function and inhibit the inflammatory reaction that usually develops in response to the presence of meconium or other injurious substances in the respiratory pathway. Although many of the examples focus on the use of one preferred embodiment -- e.g., a synthetic peptide-containing exogenous surfactant -- it is expressly to be understood that other surfactant-containing lavage compositions may be used according to the disclosed methods. Exemplary formulations for, and methods of using, surfactants are also disclosed in the present specification.

15

The following examples are intended to illustrate, but not limit, the present invention.

EXAMPLES

20 1. Preparation of Surfactant Compositions

Materials. 1,2-dipalmitoyl phosphatidylcholine (DPPC) and 1-palmitoyl, 2-oleoyl phosphatidylglycerol (POPG), and palmitic acid (PA) were obtained from Avanti Polar Lipids Inc. (Birmingham, AL). L- α -Dipalmitoyl-[dipalmitoyl-1- 14 C]-phosphatidylcholine (14 C-DDC) was obtained from New England Nuclear (Boston, MA). KL₄ peptide with the amino acid sequence KLLLLKLLLLLKLLLLKLLLLLK was synthesized as described herein or obtained from the R.W. Johnson Pharmaceutical Research Institute (La Jolla, CA). All salts, buffers and organic solvents used were of the highest grade available.

30

Procedures. Synthesis of a peptide of the present invention -- e.g., KL₄ -- may be carried out according to a

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variety of known methods of synthesis. The following procedure is described as exemplary. KL₄ peptide (9 mg), DPPC (225 mg), POPG (75 mg) and PA (45 mg) were dissolved in 2.5 milliliters (ml) of 95% ethanol at 45°C. This solution was then added to
5 7.5 ml of distilled H₂O at 45°C with rapid vortexing and 2 ml of 500 mM NaCl, 250 mM. Tris-acetate pH 7.2 was subsequently added. The resulting milky suspension was stirred at 37°C for 15 minutes and the ethanol present was then removed by dialysis (Spectrapor 2; 13,000 mol. wt. cutoff) against 100 volumes of
10 130 mM NaCl, 20 mM Tris-acetate pH 7.2 buffer at 37°C. Dialysis was continued for 48 hours with two changes of the dialysis solution.

Alternatively, the following procedure is also useful in synthesizing batches of peptide -- e.g., KL₄ peptide -- used as
15 described herein. Chemicals and reagents used in the synthesis of surfactant peptides include the following:

t-Boc-L-lysine(Cl-Z) PAM-resin (t-Boc-L-Lys(Cl-Z);
Applied Biosystems, Foster City, CA);
a-Boc-ε-(2-Chloro-CBZ)-L-Lysine (Bachem, San Diego, CA);
20 N-Boc-L-Leucine-H₂O (N-Boc-L-Leu; Bachem);
Dichloromethane (DCM; EM Science, Gibbstown, NJ, or Fisher, Pittsburgh, PA);
Trifluoroacetic acid (TFA; Halocarbon);
Diisopropylethylamine (DIEA; Aldrich, Aldrich, MI);
25 N,N-Dimethylformamide (DMF; EM Science, Gibbstown, NJ);
Dimethylsulfoxide (DMSO; Aldrich);
N-Methylpyrrolidone (NMP; Burdick & Jackson, Muskegon, MI);
30 1-Hydroxybenzotriazole hydrate (HOBt; Aldrich);
1,3-Dicyclohexylcarbodiimide (DCC; Aldrich);
Acetic anhydride (Ac₂O; Mallinckrodt, St. Louis, MO); and

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Hydrogen fluoride (HF; Air Products, Allentown, PA).

One means of synthesizing KL₄ peptide is performed on a Coupler 296 Peptide Synthesizer (Vega Biotechnologies, Tucson, AZ) using the Merrifield method (see Figure 1). A "typical" synthesis is described as follows. Chain elongation was carried out on 100 g of lysine PAM-resin by the procedure described in Table 2 below. All steps except steps 7, 10 and 11 were done automatically.

10

Table 2

Program for a Cycle Using the HOBt Active Ester Procedure

	<u>Step</u>	<u>Reagent</u>	<u>Time</u>	<u>Volume</u>
	1	50% TFA/CH ₂ Cl ₂	1x2 min	1.8 liters
15	2	50% TFA/CH ₂ Cl ₂	1x20 min	1.5 liters
	3	CH ₂ Cl ₂	5x20 sec	1.7 liters
	4	5% DIEA/CH ₂ Cl ₂	1x2 min	1.7 liters
	5	5% DIEA/NMP	1x3 min	1.7 liters
	6	DMF	5x30 sec	1.7 liters
20	7	BOC AA-HOBt active ester	1x39 min	1.0 liters
	8	DIEA/DMSO (195 ml/285 ml)	1x21 min	0.5 liters
	9	DMF	3x30 sec	1.7 liters
25	10	10% Ac ₂ O/ 5% DIEA/NMP	1x8 min	2.0 liters
	11	CH ₂ Cl ₂	3x30 sec	1.7 liters

30

While the peptide-resin was being deprotected, the appropriate amino acid derivative was being made. The appropriate amino acid was dissolved in one (1) liter of NMP. After a clear solution was obtained, HOBt was added to the

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solution. When the HOBt was dissolved, DCC was added to the solution. This solution was left stirring for one (1) hour at room temperature. During this one hour of stirring, a by-product formed, didyclohexylurea (a white precipitate). This
5 by-product was filtered off through a buchner funnel using Whatman's #1 filter paper. The filtrate was then added manually to the contents of the Vega 296 reaction vessel at step No. 7.

The synthesizer was then programmed to stop after the completion of step No. 9. Aliquots of the peptide resin were
10 subjected to the quantitative ninhydrin test of Sarin et al. (Applied Biosystems 431A user manual, Appendix A). The coupling efficiencies were good throughout the entire synthesis. The unreacted peptide resin was acetylated after leucine 12 (cycle 9) and after leucine 5 (cycle 16). After each acetylation, the
15 peptide resin was washed with dichloromethane (see Table 2, step 11).

At the end of the synthesis, the completed peptide resin was deprotected (removal of the Boc group) by completing steps 1-3 of the program (see Table 2). The deprotected peptide resin
20 was then washed with ample volumes of absolute ethanol and dried in vacuo over P_2O_5 . The weight of the dried, deprotected peptide resin was 256.48 grams. Since the batch was started with 100 g of t-Boc-Lysine (Cl-Z) OCH_2 PAM resin at a substitution of 0.64 mmoles/gram, the load corresponded to 64 mmoles. Subtracting
25 out the initial 100 grams of resin, the weight gain was 156.48 grams. The molecular weight of the nascent protected peptide (excluding the C-terminal lysine anchored onto the resin) was 3011.604 g/mole.

HF Cleavage. The 256.48 gram lot of peptide resin was
30 treated with hydrogen fluoride (HF) in three large aliquots. A Type V HF-Reaction Apparatus from Peninsula Laboratories (Belmont, CA) was used for the cleavage of the peptide resin

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using liquid hydrogen fluoride. the anisole was distilled before use. HF was used without any treatment. Dry ice, isopropanol and liquid nitrogen are required for cooling purposes.

- 5 For the first HF, approximately 88 g of the KL₄ peptide resin was placed into the one-liter reaction vessel with a magnetic stir bar. Twenty-five ml of distilled anisole was added to the peptide resin. After the entire system was assembled and leak-tested, HF was condensed into the reaction
- 10 vessel until the overall level reached about 300 ml. Cleavage of the peptide from the resin was allowed to proceed for one hour at -4°C. Partial removal of HF was done by water aspirator for 1-2 hours. After the 1-2 hours, the rest of the HF was removed by high vacuum (mechanical vacuum pump) for 1-2 hours.
- 15 The temperature of the reaction vessel remained at -4°C throughout the HF removal process.

The HF apparatus was then equilibrated to atmospheric pressure and an oily sludge was found at the bottom of the reaction vessel. Cold anhydrous ether (700 ml, prechilled to -

20 20°C) was added to the contents of the reaction vessel. The resin clumps were triturated with ether using a glass rod. The ether was decanted after the resin settled. The resin was then washed with 500 ml of room temperature anhydrous ether and allowed to stir for about 5 min. The ether was decanted after

25 the resin settled. The resin was washed until it became free-flowing (4-5 total washes). The resin was left in the fume hood to dry overnight.

The resulting dried HF-treated resin was then weighed and stored in the freezer. 1.021 grams of the dried HF-treated

30 resin was removed and extracted with 50 ml of 50% acetic acid/water and allowed to stir for 30 min. The resin was filtered through a coarse sintered glass funnel, and the

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filtrate was collected in a lyophilizing jar. The filtrate was diluted with approximately 200 ml of water, shell frozen, and placed on the lyophilizer. The one (1) gram of extracted HF-treated resin yielded 569 mg of crude peptide. The following table summarizes the large scale HF treatments of the remaining KL₄ peptide resin.

				Total Volume
HF#	Wt. of Resin	Amt. of Anisole	(HF+Anisole+Resin)	
10 1	88.07 g	25 ml	300 ml	
2	85.99 g	25 ml	300 ml	
3	79.35 g	25 ml	300 ml	

All of the HF-treated resins were stored in the freezer.

15 *Purification.* The peptide was purified using a Dorr-Oliver Model B preparative HPLC (Dorr-Oliver, Inc., Milford, CT). This unit was connected to a Linear Model 204 spectrophotometer and Kipp and Zonen dual channel recorder. This preparative HPLC was interfaced with a Waters KIL250 Column Module (Waters Associates, Milford, MA) containing a radially compressed 10x60 cm cartridge filled with Vydac C₄ support, 15-20 microns, and 300 A pore size (Vydac, Hesperia, CA). Solvent "A" consisted of 0.1% HOAc in water, and solvent "B" consisted of 0.1% HOAc in acetonitrile. The flow rate was set at 400 ml/min, the cartridge was compressed to 150-200 psi, and the preparative HPLC system back pressure was at 550-600 psi.

For the first Dorr-Oliver run, 20 g of the HF treated resin from HF#1 was extracted in 500 ml of glacial acetic acid for five minutes. Water (500 ml) was added to the resin/acetic acid mixture. This 50% acetic acid/water solution was stirred for an additional 25 minutes. The resin was filtered off with a coarse sintered glass funnel. The peptide-containing filtrate was

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saved and loaded onto the Dorr-Oliver. The HPLC gradient used was 1-40% "B" in 45 minutes, then held isocratically for seven minutes. At this point, the percent "B" was increased 1% per minute to a final percentage of 44% (not shown).

5 Fractions were collected manually and were analyzed by HPLC. All fractions that met a purity of $\geq 95\%$ were pooled together and stored in a large glass container. This material was subsequently referred to as "BPS #1." All fractions that had the desired component, but did not meet the 95% or better
10 purity, were collected and later recycled. At least 10 additional preparative HPLC runs were performed on the Dorr-Oliver unit (data not shown).

Reverse Osmosis, Lyophilization. The total volume of BPS #1 was approximately 60 liters. Reverse osmosis was used to
15 concentrate the peptide solution to a final volume of two liters. A Millipore Model 6015 Reverse Osmosis Unit with an R74A membrane to retain the peptide was used. The resulting two liters of BPS #1 were filtered through a buchner funnel using two pieces of Whatman #1 filter paper, divided into
20 approximately 11 lyophilizing jars and diluted with equal volumes of water. The lyophilizing jars were shell-frozen and lyophilized. The total weight of dry KL₄ peptide at the end of the procedure was 40.25g.

Re-lyophilization. It has been found that different
25 lyophilizing conditions (e.g. peptide concentration, composition of solvents to be lyophilized, length of the lyophilization step, shelf temperature, etc.) can result in dried preparations having differing solubility characteristics. It is desirable that the dry KL₄ peptide be soluble in a chloroform: methanol
30 (1:1) solution at 1 mg/ml and $\geq 90\%$ soluble at 10 mg/ml. If these criteria are not met at the end of the lyophilization step noted above, the peptide can be re-lyophilized. A typical re-

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lyophilization is described as follows.

Approximately 5g of peptide is slowly added to two liters of acetonitrile stirring in a glass flask. After approximately one minute, three liters of Milli-Q water is added, followed by
5 50 ml of acetic acid (final concentration of acetic acid = 1%). This is stirred for three days at 37°C, filtered through Whatman #1 filter paper in a buchner funnel, and placed into a lyophilization jar. It is then shell frozen using dry ice and isopropyl alcohol and placed on the lyophilizer. Lyophilization
10 time may vary from three to seven days. The final dry product is then weighed, packaged, and aliquots taken for solubility and chemical analyses.

2. Pharmaceutical Formulations

15 Surfactant compositions are formulated to contain 40 mg/mL total phospholipid, with a composition based on the following formula:

$PL_T = \text{total phospholipid} = \text{DPPC} + \text{POPG}$

3 DPPC:1 POPG

20 1 PL_T :0.15 PA:0.03 peptide.

Using the foregoing formula, the preferred composition per mL of finished product is essentially as follows:

	<u>Component</u>	<u>Amount per mL</u>
25	DPPC	30.0 mg
	POPG	10.0 mg
	PA	6.0 mg
	Peptide	1.2 mg

30 In addition, with regard to the buffer system/suspension, the composition may further comprise, per mL of finished product:

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	<u>Component</u>	<u>Amount per mL</u>
	Tromethamine, USP	2.42 mg
5	Glacial acetic acid or NaOH, NF	quantity sufficient to adjust tromethamine buffer to pH 7.7
	NaCl, USP	7.6 mg
	Water for inject., USP	quantity sufficient to 1.0 mL

10

A Tham buffer system is prepared essentially as follows.
0.37 ml of Tham solution (tromethamine injection, NDC 0074-1593-04, Abbott Laboratories, North Chicago, IL), pH adjusted with acetic acid (AR Select, ACS, Mallinckrodt, Paris, KY) to a pH of
15 7.2 \pm 0.5, is admixed with 0.33 ml saline (0.9% sodium chloride injection, USP, Abbott Laboratories) and 0.30 ml water (sterile water for injection, USP, Abbott Laboratories) and is sterile-filtered.

20 3. In Vitro Assessment of Polypeptide Surfactant Activity

Measurement of Surfactant Activity. Measurements of surface pressure across an air-liquid interface (expressed in negative cm of H₂O pressure) at minimal (γ min) bubble radius were determined at various times using the pulsating bubble
25 technique described by Enhorning, J. Appl. Physiol., 43:198-203 (1977).

Briefly, the Enhorning Surfactometer (Surfactometer International, Toronto, Ontario) measures the pressure gradient (ΔP) across a liquid-air interface of a bubble that pulsates at
30 a rate of 20 cycles/min between a maximal (0.55 mm) and minimal (0.4 mm) radius. The bubble, formed in a 37°C, water-enclosed, 20- μ l sample chamber, is monitored through a microscopic optic while the pressure changes are recorded on a strip chart recorder calibrated for 0 and -2 cm H₂O.

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Determination of Composite Hydrophobicity Value. The composite hydrophobicity value of each peptide was determined by assigning to each amino acid residue in a peptide its corresponding hydrophilicity value as described in Table 1 of Hopp et al, PNAS USA, 78:3824-3829 (1981), which disclosure is incorporated herein by reference. For a given peptide, the hydrophilicity values were summed, the sum representing the composite hydrophobicity value.

Preparation of Surfactants. After admixture with solvent, each peptide was combined with phospholipids (DPPC:PG), 3:1 to form a surfactant according to one of the following methods.

Method A was accomplished by admixing 16 μ l of peptide/solvent admixture (40 μ g peptide) with 100 μ l of chloroform containing 400 μ g phospholipids, agitating the admixture for about 10 at 37°C to form a peptide/phospholipid admixture. Chloroform was removed from the peptide/phospholipid admixture by drying under N₂. The surfactant thus formed was then admixed with 90 μ l of H₂O and gently agitated for about 10 minutes at 37°C. Subsequently, 10 μ l of 9% NaCl was admixed to the surfactant-containing solution.

Method B was accomplished by first placing 100 μ l of chloroform containing 400 μ g of phospholipids in a glass tube and removing the chloroform by drying under N₂ for about 10 minutes at 37°C. Sixteen μ l of peptide/solvent admixture and 74 μ l H₂O were admixed with the dried phospholipids, and then gently agitated for about 10 minutes at 37°C. To the surfactant thus formed was admixed 10 μ l of 9% NaCl.

Method C was accomplished by first maintaining the polypeptide-PL admixture at 43°C for 10 minutes, after which time the solvents were removed from the admixture by drying under N₂. When needed, admixtures were further dried by 15 minutes exposure to vacuum to form a dried polypeptide-PL

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admixture. Water was then admixed with each dried admixture in an amount calculated to equal 90% of the volume necessary to give a final PL concentration of either 4 or 10 mg/ml (as indicated in Table 4) to form a second admixture. This second
5 admixture was maintained for one hour at 43°C with agitation. Subsequently, a volume of 6% NaCl equal to 10% of the volume necessary to give the desired PL concentration was admixed with the second admixture and the resulting final admixture was maintained for 10 minutes at 43°C. In most cases, the final
10 admixture was subjected to a last step of 3 cycles of freezing and thawing.

Results. The surfactants illustrated in Table 3 were prepared as indicated in the table.

Table 3

5	Peptide/ SEQ ID NO ⁽¹⁾	Solvent	(2) Admixture Formed	(3) Phospholipid Admixture Method	(4) Composite Hydrophobicity	
					Value	
	p1-15 / 12	n-propyl alcohol	suspension	A	-16.7	
	p11-25 / 12	H ₂ O	solution	B	+ 1.7	
10	p21-35 / 12	Chloroform	suspension	A	- 9.2	
	p31-45 / 12	H ₂ O	solution	B	- 9.9	
	p41-55 / 12	H ₂ O	solution	B	- 5.4	
	p51-65 / 12	H ₂ O	suspension	B	- 2.2	
	p61-75 / 12	methanol	suspension	A	- 9.9	
15	p71-81 / 12	H ₂ O	suspension	B	+ 3.9	
	p74-81 / 12	H ₂ O	solution	B	+ 3.7	
	p66-81 / 12	methanol:H ₂ O	suspension	A	- 1.0	
	p52-81 / 12	methanol:H ₂ O	suspension	A	- 6.2	

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20 (1) All the identified peptides have an amino acid residue sequence corresponding to a portion of SEQ ID NO 12; for example, peptide p1-15 comprises amino acid residue nos. 1-15 of SEQ ID NO 12.

(2) Each polypeptide was admixed with the indicated solvent to achieve a concentration of 2.5 µg of peptide per µl solvent.

25 (3) The letters indicate the surfactant preparation method used. Those methods are described above.

(4) The composite hydrophobicity value of each peptide was determined as described above.

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Each of the surfactants identified in Table 3 was assayed for surfactant activity as evidenced by their ability to reduce surface tension *in vitro* using the "bubble assay" of Enhorning as described above.

5 The results of this study (data not shown) indicate that a subject polypeptide, when admixed with pharmaceutically acceptable phospholipids, forms a pulmonary surfactant that has greater surfactant activity than the phospholipids alone, as evidenced by the lower ΔP values. Typically 10% to 80% lower ΔP
10 values were obtained using the polypeptides. It should be noted that the eight amino acid residue control peptide p74-81, which does not conform to the teachings of the present invention, did not form a PS having a greater activity than the phospholipid alone, thus indicating that amino acid residue length is a
15 critical feature.

The surfactant activity of additional exemplary polypeptides of this invention was studied using the "bubble assay" as described above. The results of the study are illustrated below in Table 4.

20 Each polypeptide was admixed with the indicated solvent at a concentration of 2.5 mg of polypeptide per ml of solvent. The resulting admixture was observed to determine whether a solution or a suspension of insoluble polypeptide was formed. Those admixtures forming a suspension were further admixed by water
25 bath sonication for 10 seconds to form a very fine suspension, sufficient for pipetting using glass pipettes.

After admixture with solvent, each peptide was admixed with phospholipids (PL), DPPC:PG, 3:1, in chloroform in a glass tube so that the amount of polypeptide added equaled one-tenth (10%
30 by weight) of the amount of PL added, to form a surfactant according to either method A, B or C.

Each of the surfactants was then assayed for surfactant

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activity as evidenced by their ability to reduce surface tension in vitro in the bubble assay performed as described above. The pressure gradient (ΔP) is a measure of surfactant activity in the polypeptide-PL third admixture which was determined using an

5 Enhorning Surfactometer as described above. Measurements were obtained at time points of 15 seconds (15"), 1 minute (1') and 5 minutes (5') and are expressed as a mean of three independent measurements of the indicated polypeptide-PL admixture.

Pressure gradient measurements for comparable samples of PL

10 alone (PL) and natural human surfactants were determined as controls. The results of this study are shown in Table 4.

Table 4

Peptide ⁽¹⁾	Solvent	(2) Admixture Formed suspension	(3) Phospholipid Admixture Method	(4) Conc. of PL mg/ml	(5) Pressure Gradient		
					15"	1"	5"
p1-15	N-propanol		A	4	0.94	0.82	0.48
p36-81	50% chloroform 0% methanol	suspension	C+	10	0.90	0.87	0.79
p46-76	64% chloroform 36% methanol	solution	C+	10	0.90	0.80	0.62
p51-72	75% chloroform 25% methanol	suspension	C+	10	1.15	0.76	0.33
p51-76	37% chloroform 63% methanol	solution	C+	10	0.99	0.91	0.42
p51-80	45% chloroform 55% methanol	solution	C+	10	0.92	0.89	0.48
p51-81	50% chloroform 50% methanol	suspension	C+	10	0.94	0.86	0.64
p52-81	67% DMF 33% chloroform	solution	A	4	1.33	1.19	0.96

p54-72	76% chloroform 24% methanol	suspension	C+	10	1.28	0.92	0.38
p54-76	71% chloroform 24% methanol	suspension	C+	10	0.92	0.82	0.23
p59-81	68% chloroform 32% methanol	solution	C-	4	1.08	1.02	0.75
p66-81	40% DMF 60% chloroform	suspension	A	4	1.22	1.11	0.84
p74-81	water	solution	B	4	2.37	2.32	2.31
DL4 (31 mer)	47% chloroform 53% methanol	solution	C-	4	2.00	1.80	1.30
RL4	32% chloroform 68% methanol	solution	C-	4	0.58	0.65	0.33
RL8	19% chloroform 81% methanol	suspension	C+	10	0.68	0.69	0.19
RL7	49% chloroform 51% methanol	solution	C-	4	1.65	1.25	1.00
RCL-1	79% chloroform 21% methanol	suspension	C+	10	0.50	0.59	0.06
RCL-2	67% chloroform 33% methanol	suspension	C+	10	0.00	0.00	0.00

RCL-3	75% chloroform 25% methanol	suspension	C+	10	0.55	0.51	0.33
PL			C+	10	>2.50	>2.50	2.33
Natural Human Surfactant				10	1.06	0.89	0.79

(1) All the identified peptides have an amino acid residue sequence corresponding to a portion of SEQ ID NO 12; for example, peptide p1-15 comprises amino acid residue nos. 1-15 of SEQ ID NO 12.

(2) Whether the initial admixture of peptide was a solution or a suspension is indicated.

(3) The letters indicate the surfactant preparation method used. Those methods are described above. A "+" indicates that the final admixture was subjected to a last step of 3 cycles of freezing and thawing. A "-" indicates the step was not performed.

(4) Concentration ("Conc.") of phospholipid (PL) in the final third admixture is indicated in milligrams PL per milliliter admixture (mg/ml).

(5) The pressure gradient is a measure of surfactant activity in the polypeptide-PL final admixture as determined using an Enhorning Surfactometer as described in Example 3. Measurements were obtained at three points of 15 seconds (15"), 1 minute (1') and 5 minutes (5') and are expressed as a mean of 3 independent measurements of the indicated polypeptide-PL admixture. Pressure gradient measurements for comparable samples of PL alone (PL) and natural human surfactant are also shown.

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These results indicate that a subject polypeptide, when admixed with pharmaceutically acceptable phospholipids, forms a pulmonary surfactant that has a greater surfactant activity than the phospholipids alone, as demonstrated by the lower surface pressures obtained.

4. In Vivo Assessment of Surfactant Activity in a Rabbit Model

Preparation of Surfactants. A subject polypeptide was first admixed with solvent as described in Example 3. The resulting admixture was further admixed with phospholipid (PL) so that the amount of polypeptide added was either 3%, 7% or 10% by weight of the amount of PL added as indicated below. The final polypeptide, PL admixture (surfactant) was formed according to method C using the final freeze thaw step as described in detail in the "Preparation of Surfactants" section in Example 3, except that the final admixture had a concentration of 20 mg phospholipid per ml of final admixture.

Instillation Protocols.

Protocol 1: Fetal rabbits were treated by injection into the trachea of a 0.1 ml solution that contained either a synthetic surfactant prepared in Example 4 or either 2 mg of native surfactant prepared as described in Example 1 of U.S. Patent No. 5,260,273 (incorporated by reference herein) or 2 mg PL.

Protocol 2: surfactant was instilled in rabbit fetal lung by injection into the trachea from a single syringe of the following three components such that the components exit the syringe in the following order: (1) 0.05 ml air; (2) 0.1 ml of a synthetic surfactant prepared in Example 4 or either 2 mg of PL or 2 mg of native surfactant; and (3) 0.1 ml air.

Protocol 3: From one syringe, a 0.1 ml aliquot of synthetic surfactant prepared as described in Example 4 (or 2 mg

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of NS or of PL), was instilled into the rabbit trachea as described above, followed by injection of 0.05 ml lactated Ringer's Solution and 0.2 ml air from a second syringe.

Protocol 4: From one syringe, 0.1 ml of a synthetic
5 surfactant prepared as described in Example 4 (or 2 mg of NS or of PL), 0.15 ml air, 0.1 ml saline, and 0.3 ml air were injected into the trachea as described above. Two subsequent aliquots of 0.3 ml air were given.

Protocol 5: Fetal rabbits were treated by injection into
10 the trachea from a single syringe the following four components such that the four components exit the syringe upon injection in the order listed: (1) 0.2 ml solution that contains either a synthetic surfactant prepared in Example 4 or either 4 mg of native surfactant, or 4 mg PL; (2) a 0.15 ml volume of air; (3)
15 a 0.1 ml normal saline solution; and (4) a 0.3 ml volume of air. The above injection was then repeated 15 minutes after the first injection.

Protocol 6: Rabbits were treated as described in Protocol 5, except that two subsequent aliquots of 0.3 ml air were given
20 following the initial instillation and no additional instillation was given at 15 min.

Fetal Rabbit Model for Studying Surfactant Activity

The surfactant activity of exemplary polypeptides of this invention was studied using the methods described in detail
25 previously by Revak et al, Am. Rev. Respir. Dis., 134:1258-1256 (1986), with the exceptions noted hereinbelow.

Twenty-seven day gestation fetal rabbits were delivered by hysterotomy and immediately injected with 0.05 ml Norcuron (Organon, Inc., NJ) to prevent spontaneous breathing. The fetal
30 rabbits were then weighed and a small cannula was inserted into the trachea by tracheotomy. surfactant prepared as described above was then instilled into the fetal rabbit lung by one of

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the above instillation protocols.

Following instillation the rabbit was placed in a specially designed plethysmograph (containing a Celesco transducer) connected to a ventilator (Baby Bird, Baby Bird Corp., Palm Springs, CA) and the instilled lung was ventilated at a rate of 30 cycles per minute with a peak inspiratory pressure of 25 cm H₂O, a positive end expiratory pressure (PEEP) of 4 cm H₂O and an inspiratory time of 0.5 seconds. In some studies, dynamic compliance measurements were made at various times throughout the ventilation procedure. In others, static compliance measurements were made following ventilation.

Static compliance measurements were made after 30 minutes of ventilation. The animals were removed from the ventilator and the lungs were degassed at -20 cm H₂O in a bell jar under vacuum. Thereafter, the lungs were first inflated and then deflated through a T-connector attached to a tracheostomy tube. The volume of air required to reach static pressures of 5, 10, 15, 20, 25 and 30 cm H₂O was measured during both inflation and deflation phases to generate static pressure to volume curves as a measure of static compliance.

Using the plethysmograph, dynamic compliance measurements were made at various times throughout a 60 minute ventilation period. Computer-assisted data analysis resulted in compliance data expressed as ml of air per cm H₂O per gram of body weight at each time point. Compliance was calculated by the formula below.

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

$$\Delta P_{tp} = (C)^{-1} \bullet (\Delta V) + (R) \bullet (F)$$

$$P_{tp} = \text{transpulmonary pressure}$$

$$C = \text{compliance (elastic component - relates change in volume to pressure)}$$

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R = resistance (relates flow to pressure)

F = flow

5 V = volume = the integral of flow with respect to
time

The above equation was solved with a multiple linear regression for C and R. The compliance (C) represents the
10 elastic nature of the lungs and the resistance (R) represents the pressure necessary to overcome the resistance to the flow of gas into and out of the lungs.

Results. Static compliance data was collected using instillation protocols 1 and 5. Improved lung compliance was
15 seen in all lungs treated with natural surfactant or with the surfactants of the present invention tested as compared with those lungs treated with phospholipids (PL) alone, with one exception. The surfactant prepared using p1-15 did not produce improved lung compliance over PL alone when measured by static
20 compliance.

The results of the dynamic compliance studies are illustrated in Table 5.

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Table 5

Dynamic Compliance
in ml air/cm H₂O
(g body weight x 10⁶)

% Peptide Compound	To PL	Minutes after Surfactant Instillation						Sample ¹ Given By Protocol #
		10	20	30	40	50	60	
<u>PL</u>		7	8	7	10	11	15	4
		24	22	23	23	22	20	4
		15	16	17	18	21	29	4
<u>NS</u>		265	251	168	186	173	147*	4
		418	388	405	288	237	*	4
		155	176	172		172	179	4
<u>p36-81</u>	5%			255			146*	3
	5%			245			291	3
	10%			154			1,162	2
	10%			252			623	2
<u>p52-81</u>	5%			517			226*	3
	5%			434			55*	3
	10%			195			1,243	2
	10%			43			1,690	2

p51-76

10%	33	22	56	87	124	85	4
10%	10	11	186	358	141	144*	4
10%	15	36	109	241	264	301	4

p51-80

10%	17	41	52	78	99	208	4
10%	76	94	149	149	217	308	4
10%	23	71	130	156	182	109*	4

1 Prior to instillation into the rabbits, these samples were filtered through a 25 micron filter.

* A decrease in compliance with time may indicate the development of pneumothorax.

As shown in Table 5, each of the surfactants of this invention and natural surfactant improved dynamic compliance values in comparison to phospholipid alone.

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Discussion. The *in vivo* compliance studies demonstrate that the use of a number of exemplary surfactants of this invention resulted in enhanced compliance in comparison to phospholipid alone for each of the assayed surfactants. Thus, the proteins and polypeptides of this invention when admixed with pharmaceutically acceptable phospholipids form surfactants that have greater surfactant activity than phospholipid alone. Use of the surfactants is advantageous in producing improved compliance values *in vivo*.

10

5. Use of Pulmonary Surfactant as a Therapeutic Agent in Meconium Aspiration Syndrome

In view of the variability in efficacy achieved by using exogenous surfactant given as a bolus in the treatment of experimental and clinical Meconium Aspiration Syndrome (MAS), and in view of the somewhat equivocal results achieved when standard lavage methods are used, alternative therapeutic modalities are clearly needed. Therefore, the compositions and methods disclosed herein provide a very real improvement over therapies and compositions described in the art relating to MAS.

In models of MAS of human infants, adult rabbits and newborn rhesus monkeys received intratracheal instillation of human meconium to induce pulmonary injury. The results presented herein indicate that pulmonary function in two models of severe meconium injury respond rapidly to bronchoalveolar lavages (BAL) containing dilute KL₄-Surfactant when administered as described.

a. Materials and Methods

30

I. Animal Models

Adult NZW rabbits, approximately 2.5 kg in weight and rhesus monkeys (*Macaca mulatta*) delivered at full

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term by Caesarean section and weighing approximately 520 gms were employed.

The rabbits were studied at The Scripps Research Institute (La Jolla, CA) and the rhesus monkeys were examined at the California Primate Research Center (Davis, CA). The studies were approved by the Animal Research Committee of The Scripps Research Institute, and the Animal Use and Care Committee, UC Davis. All studies conformed to the requirements of the Animal Welfare Act and National Institutes of Health Guidelines.

10

ii. Meconium Preparation

The first stool passed by human infants was collected and stored frozen until pools were made representing meconium from 5-11 infants. Sterile water was added until a stirrable slurry was achieved. After freezing, the mixture was lyophilized and a dry weight obtained. Sterile saline was added in amounts calculated to yield a concentration of 50 mg (dry weight)/ml. The stock solutions were homogenized in a blender, filtered through gauze to remove particulate material and stored frozen until diluted for use. For most samples, the dry weight was 25-30% of the original wet weight. Meconium quantities are expressed as dry weight.

15

20

iii. KL₄-Surfactant

KL₄-Surfactant, a synthetic peptide-containing surfactant consisting of dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol (POPG), palmitic acid (PA), and a synthetic peptide of the sequence KLLLLKLLLLKLLLLKLLLLK, was prepared, as described previously (Cochrane et al, Am J Resp & Crit Care Med, 152:404-410, 1996; Revak et al, Ped. Res., 39:715-724, 1996).

25

30

Briefly, synthetic peptides, including KL₄, were synthesized

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using a solid phase peptide synthesizer and provided by R.W. Johnson Pharmaceutical Research Institute (La Jolla, CA). DPPC, POPG and palmitic acid were obtained from Avanti Polar Lipids (Birmingham, AL). Peptide-containing surfactant was prepared by
5 mixing DPPC and POPG in a 3:1 ratio by weight with PA in which PA is present at 15% w/w with the lipids, and dissolving the mixture in organic solvent. Thereafter, the peptide was dissolved in organic solvent, and admixed with the lipid mixture at a ratio of 3% w/w of peptide per phospholipid
10 weight. Organic solvents were removed by evaporation under nitrogen. Tris buffer was then added to form a liposomal surfactant composition at pH 7.2-7.4 and 250-350 mosmol/kg. Dilutions with saline were made as needed from the stock solution.

15

iv. Biochemical Assays

Protein assays were performed using a BCA reagent kit (Pierce, Rockford, Illinois) according to the manufacturer's instructions. Myeloperoxidase (MPO) was measured using a
20 modification of the o-dianisidine method described by Steinman and Cohn for the measurement of horseradish peroxidase (Steinman et al, J. Cell Biol., 55:186-204, 1972). Typically, 200 μ l of 125 μ g/ml o-dianisidine in 100 mM citrate buffer pH 6.0 were added to 20 μ l of sample.

25 The change in absorbance at 405 nm over a 10 min period following the addition of 20 μ l of 2 mM H₂O₂ was proportional to the amount of MPO present. A standard reference solution which caused an absorbance change of approximately 0.072 units/ μ l/10 min was used. One unit of MPO activity was defined as the
30 activity in 1 μ l of the reference solution.

Rabbit and monkey IL-8 were quantitated in lavage washes by a previously described ELISA method (Schraufstatter et al, J.

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Immunol., 151:6418-6428, 1993).

Surfactant was isolated from rabbit or monkey lung lavage fluids by taking the supernatant from a 5 minute, 1000 rpm spin (which removed cells and debris) and subjecting it to a 1 hour spin at 40,000 g at 4°C. The precipitate from this high-speed spin was resuspended in 1/20 the original volume of normal saline and quantitated as to the amount of phospholipid present by a modification of the method of Rouser et al, Lipids, 5:494-496 (1970).

Meconium was quantitated spectrophotometrically. Samples were centrifuged at 40,000 x g for 1 hour. The optical density (OD) of the supernatant (or dilutions in saline) was read at 260 and 300 nm and the following formula applied: $OD_{300} - (.13)(OD_{260})$. This formula was derived empirically from spectral analyses of multiple rabbit and monkey lavage samples with and without meconium; it was found to yield values of approximately zero for samples not containing meconium and a linear relationship was found to exist for solutions containing from 1 to 1600 µg/ml meconium.

Lavage samples from animals with pulmonary inflammation, determined microscopically, were found to have a unique absorption peak at approximately 400-405 nm which was not present in lavage fluids of normal animals. Using this observation and correcting for absorption of proteins with peaks <300 nm, an arbitrary "Inflammatory Index" was defined as $OD_{400} - (.45)(OD_{305})$.

Cells present in lavage wash samples were evaluated by standard cell staining and counting techniques to identify PMN's and RBC's (erythrocytes).

30

v. Surface tension-lowering assay

The ability of surfactant to lower surface

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tension at an air-liquid interface was measured using a pulsating bubble surfactometer as described previously (Revak et al, Am. Rev. Respir. Dis., 134:1258-1265, 1986). Samples were diluted to 3 mg/ml phospholipid before assay.

5

vi. Compliance assays

Compliance assays were performed on rabbits prior to instillation of meconium, at 0.9 hours after meconium, i.e., just prior to treatment, and at about 5 hours after meconium
10 instillation. Rabbits were treated with vecuronium bromide (0.1 ml/kg IV), briefly removed from the ventilator, connected to a pressure/volume monitoring circuit, with recording of volumes of air corresponding to increments of 5 cm H₂O pressure up to and down from 35 cm H₂O.

15

vii. Postmortem Examination

Rabbits and rhesus monkeys were sacrificed with IV barbiturate. The thorax was opened and heart and lungs removed *en bloc* with the trachea clamped under 10 cm H₂O
20 pressure. Gross examination was performed with the tracheal pressure at both 10 cm H₂O and atmospheric pressure. One lung was placed in 10% Zn- formalin following ipsilateral ligation of the bronchus at 10 cm H₂O pressure for microscopic examination. The other lung received two lavages of approximately 2 ml/kg
25 sterile saline each, placed in the same segment.

After removal of 0.1 ml for cell counts, lavage fluids were centrifuged at 1000 x g 5 min to remove cells, and then 40,000 x g 60 min to isolate the surfactant and provide lavage fluid for biochemical studies. For counts of polymorphonuclear leukocytes
30 (PMNs) in histologic sections of the lung, a straight line was drawn on the coverslip within 2 mm of the mainstem bronchus of the lower lobe, traversing the entire section as a cross-section

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of the lung. Microscopic counts were then performed along the line from one pleural edge to the other. This method was chosen in view of the consistent injury produced by meconium to this area of the lower lobe and the consistency of treatment with KL₄-
5 Surfactant or saline to this region of the lung.

viii. Statistical Analyses

Groups were compared using a two group unpaired t test. Statistical difference was taken as $p < 0.05$.

10

b. Adult Rabbit Lavage Model and Instillation Protocols

Rabbits were divided into 4 treatment groups, as follows. Group 1 rabbits received bronchoalveolar lavages (BAL) with dilute KL₄-Surfactant. Group 2 animals received lavages
15 with equal volumes of sterile saline. Group 3 rabbits received a single intratracheal bolus of KL₄-Surfactant, 100 mg/kg. Group 4 animals received no treatment -- i.e., no lavages or boluses -- at all.

As described hereinbelow, the untreated rabbits developed
20 atelectasis, a fall in compliance and in PaO₂ from approximately 500 to <100 mm Hg, and severe pulmonary inflammation between 3-5 hours after instillation of meconium. Rabbits treated by BAL with dilute KL₄-Surfactant showed rapid and sustained recovery of PaO₂ to approximately 400 mm Hg within minutes, a return toward
25 normal compliance and diminished inflammation. Rabbits receiving BAL with saline failed to show recovery, and rabbits treated with a bolus of surfactant intratracheally exhibited a transient response by 1-2 hours after treatment, but then returned to the initial atelectatic collapse.

30 Rabbits were anesthetized with intramuscular (IM) Xylazine and Ketamine. Tracheostomy was performed and a 3.0 mm internal diameter endotracheal tube inserted to a position at least 1 cm

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above the carina. An arterial line for blood samples was placed in the auricular artery. All animals were then placed on a pressure-cycled ventilator (Bird; 3M, St. Paul, MN). To induce pulmonary injury, meconium was instilled intratracheally. The appropriate volume of meconium was divided into two equal portions, one given with the rabbit held at 45°C with its head up and the right side of the animal down, and the second half as before, but with the left side down.

Meconium was instilled through a cannula threaded through the endotracheal tube and reaching <0.5 cm beyond the tip of the endotracheal tube. Rabbits were placed on 100% O₂ for 10-15 min before instillation of meconium and received 100% O₂ for the duration of the study. After the meconium instillation, mechanical ventilation was begun with peak inspiratory pressure (PIP) of 25 cm H₂O, generally, and positive end expiratory pressure (PEEP) of 2 cm H₂O and ventilatory rate of 20 breaths per minute. Blood gas determinations were performed approximately 10, 30 and 50 minutes after meconium instillation. After 1 hour, the rabbits were placed into one of four treatment groups, as follows.

Group 1 rabbits received bronchoalveolar lavage with KL₄-Surfactant diluted to 2-5 mg/ml, receiving 20 ml/kg divided into two equal portions, one lavaged into the right lung, and the second half into the left lung. The rabbit was given intravenous (IV) vecuronium bromide 0.1 ml/kg to induce paralysis, found to be essential for appropriate drainage in the lavage procedure. The KL₄-Surfactant was instilled with the ventilator on PEEP alone, at a pressure of 8 cm H₂O, i.e. without air movement. The animal was held head up at approximately 45° with, first, the right side down in order to instill surfactant into the right lung. Immediately after instillation of the dilute surfactant, intermittent ventilation (IMV) was re-started

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with PIP of 25 cm H₂O and PEEP of 5 cm H₂O for five breaths.

The rabbit was then disconnected from the ventilator and the lavage-surfactant and meconium were drained by tipping the rabbit head down at 30-45°. All lavage volumes were recorded along with the time required for the procedure. Drainage was continued with gentle massage of the chest until flow slowed considerably. The total time required for the lavage procedure was approximately 90 seconds. The rabbit was immediately placed back on IMV with the same settings (PIP, 25; and PEEP, 5) for 2-5 minutes. The lavage procedure was then repeated with the left side of the rabbit held down in order to lavage the left lung. This constituted the first lavage. Repeated lavages were performed similarly, each divided between right and left lungs. As noted in the text, a final lavage was performed with KL₄-Surfactant using a concentration of KL₄-Surfactant of 10 or 15 mg/ml; alternatively, in some animals, a bolus of KL₄-Surfactant was given at 30 mg/ml, (100-150 mg/kg) in order to provide sufficient levels of retained surfactant to maintain good pulmonary function.

Group 2 rabbits received bronchoalveolar lavage with sterile saline, performed as in (1), but using equal volumes of sterile saline.

Group 3 rabbits received instillation of a bolus of KL₄-Surfactant (i.e., without lavage) at a concentration of 30 mg/ml, using 100 mg/kg divided equally between right and left lungs.

Group 4 rabbits received no treatment of the meconium injury.

I. Response of adult rabbits to intratracheal administration of varying doses of human meconium
Initial studies were performed to determine the

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response of adult rabbits to varying doses of a slurry of human meconium given intratracheally. Rabbits received the following doses of meconium (mg/kg in 5 to 7.5 ml/kg): 93.8 (n=3); 125 (n=4); 187.5 (n=7); 281.3 (n=2); 375 (n=1). While doses of 93.8 and 125 mg/kg produced a fall in PaO₂ and partial atelectasis in the lung, the effect was not consistent, and 71% of the rabbits showed signs of spontaneous recovery of PaO₂ by five (5) hours after instillation of the meconium.

At the dose of 187.5 mg/kg, a consistent fall in PaO₂ occurred within 1 hour of instillation of meconium and spontaneous recovery of PaO₂ by 5 hours was not observed (Figure 3). Doses higher than 187.5 mg/kg also induced a fall in PaO₂, but with death occurring in 2 of the 3 rabbits.

The dose of 187.5 mg/kg in 7.5 ml/kg was selected for further study. In these rabbits, autopsies at 5-6 hours after instillation of meconium revealed marked atelectasis of the lungs (not shown), with dark red, non-expanded areas in at least 80% of the lung. Small rims or caps of expanded lung existed in the apical region of the upper lobes and in some instances, the lower lobes, presumably due to a failure of the meconium to reach these areas. Histologically, at 1-2 hours after administration of meconium, the alveoli were collapsed, but little evidence of inflammation was observed. With PAS stain, the meconium could be detected by its bright violet color, forming fine, amorphous clumps in the alveolar spaces, generally abutting the septae. There were no obstructive plugs of meconium observed in the bronchi, presumably as a result of filtration of the meconium preparation. At 5-6 hours after meconium was administered, the lungs revealed widespread atelectasis, with dense infiltration of edema and inflammatory cells, primarily, polymorphonuclear leukocytes (PMNs), together with red blood cells (RBCs) (not shown).

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NON SOUMIS(E) AU MOMENT DU DÉPÔT

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injury (i.e., 4 hours after treatment was begun). Compliance values are the mean \pm SEM of measurements made at 30 cm H₂O pressure during the inflation portion of the measurement and are expressed as ml air/30 cm H₂O/kg. There was no statistical difference between the groups in the pre-injury or 0.9 hour post injury values. Only the KL₄-surfactant lavage group was significantly different from the untreated control group at 5.1 hours post injury.

Table 6

Compliance Values of Lungs of Rabbits Injured With
Meconium Followed by Various Forms of Treatment

Treatment:	None	Lavage	<u>KL₄-Surfactant</u>		Saline
			Bolus	Lavage	
	n	7	11	5	5
pre-injury		12.3 \pm 1.0	11.9 \pm 0.5	11.4 \pm 0.5	10.8 \pm 0.5
post injury (0.9 hr.)		1.9 \pm 0.4	2.0 \pm 0.5	2.6 \pm 0.5	1.3 \pm 0.2
post injury (5.1 hrs)		3.1 \pm 0.8	6.2 \pm 0.9	1.7 \pm 0.1	2.3 \pm 0.6

To test the effect of meconium *in vivo* on the rabbit surfactant, additional rabbits receiving 187.5 mg/kg human meconium, underwent bronchoalveolar lavage after 1 hour with saline to obtain the surfactant. The surfactant was isolated by high speed centrifugation as described above, and the activity of the residual native surfactant was determined using the pulsating bubble surfactometer at 3 mg/ml phospholipid. As shown in Table 7, the activity of surfactant was greatly diminished.

Table 7

Inhibition of Intrinsic Surfactant Activity Following
Instillation of Meconium Into Adult Rabbit Lungs

	Surface Tension	
	Minimal	Maximal
Lavage - meconium	2.9 ± 0.9	33.5 ± 0.6
Lavage + meconium	22.4 ± 1.3	56.5 ± 2.5

Each value represents the mean ± SEM of six determinations of surface tension obtained with surfactant at a concentration of 3 mg/ml isolated from lavage fluids recovered from two rabbits. Saline lavage was performed one hour after 187.5 mg/Kg of meconium was instilled into the lungs. Surface tensions are expressed in dynes/cm and were measured one minute after bubble formation in a pulsating bubble surfactometer.

As controls, three rabbits received equal volumes (5-7.5 ml/kg) of sterile saline intratracheally instead of meconium.

The effect on PaO₂ levels is shown in Figure 3. The average PaO₂ remained between 400 and 550 mm Hg over the 5 hour period, although one rabbit showed a gradual fall in PaO₂ to 249 mm Hg by 5.5 hours. Statistical difference in PaO₂ values ($p < 0.05$) was seen between the saline control and meconium-treated rabbits for all time points ≥ 1.0 hr. Compliance measurements of these rabbits fell from 14.2 to 8.0 at 0.9 hours and then recovered partially by 5.1 hours. At autopsy the lungs were diffusely expanded with 2-5 small (<0.5 cm) zones of atelectasis in the lower lobes, and with two larger zones of atelectasis, 1-2 cm in size, in the rabbit showing a gradual fall in PaO₂.

Microscopically, >90% of the lung showed expanded alveoli, but atelectatic zones were observed containing collapsed alveoli and a mild infiltration of inflammatory cells.

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ii. The effect of bronchoalveolar lavage with dilute KL₄-Surfactant on lung expansion, gas exchange and pulmonary inflammatory response in meconium-injured adult rabbits

5 Seventeen rabbits were given meconium at 187.5 mg/kg to induce (a) loss of surfactant activity in the lungs with associated collapse of the alveoli, and (b) development of inflammation at 3-5 hours after meconium instillation. Twelve of the rabbits were lavaged with KL₄-Surfactant as follows: 2-4
10 times with the KL₄-Surfactant diluted to 2-5 mg/ml and once at 10-15 mg/kg using 20 ml/kg divided equally between right and left sides as described above. The remaining 5 rabbits were similarly lavaged with equal volumes of sterile saline, rather than with KL₄-Surfactant. The recovered volumes of the
15 sequential lavages were measured and the individual lavage fluids saved for assays of meconium content. The FiO₂ was maintained at 1.0 and the ventilators adjusted to PIP of 25-28 and PEEP of 2-10, with a ventilatory rate of 20-32/min as required to maintain adequate ventilation.

20 The removal of meconium by 3 sequential lavages with dilute KL₄-Surfactant is shown in Figure 5. As noted, about 29% of the instilled meconium was removed by the first lavage, 7.5% more in the second lavage, and less than 5% in the third lavage. As will be noted below, this correlated with diminished meconium
25 observed microscopically in lung sections taken at necropsy than was observed in rabbits not lavaged. Following lavage with dilute KL₄-Surfactant, a single divided lavage using KL₄-Surfactant at 10-15 mg/ml was performed in order to assure that sufficient functional surfactant was present in the lungs. The
30 calculated average amount of KL₄-Surfactant remaining in the lungs after this final lavage was 77 ± 12 mg/kg.

 The response in PaO₂ of the rabbits to the bronchoalveolar

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lavage with KL₄-Surfactant occurred rapidly, most often within 2 minutes after the first lavage (Figure 6). The PaO₂ rose from <100 mm Hg to approximately 400 mm Hg with the rabbit ventilated at FiO₂ of 1.0. The PaO₂ remained elevated through 5 hours although a drop to a mean of about 300 mm Hg was seen 3-5 hours after instillation of the meconium.

Rabbits receiving lavage with saline instead of dilute KL₄-Surfactant failed to show improvement in gas exchange (Figure 6) although comparable amounts of meconium were removed. Increases in PEEP did not increase appreciably the PaO₂ in saline-lavaged animals. The difference in PaO₂ values between rabbits treated with KL₄-Surfactant lavage and those lavaged with saline was statistically significant at all time points following treatment.

Static compliance assays, performed at time 0, 0.9 hours after instillation of meconium, (immediately before lavage treatment), and at approximately 5 hours after injury with meconium, (i.e., approximately 4 hours after lavage treatment), are shown in Figures 4A-4D and Table 6. As noted previously, the compliance values fell after instillation of meconium. Lavage treatment with KL₄-Surfactant (Figure 4B) resulted in a significant improvement in compliance at the 5 hour time point as shown, while lavage with saline (Figure 4C) failed to restore compliance changes above those of rabbits receiving meconium alone. Compliance analyses performed in 4 rabbits at an intermediate time point, (2.6 hours after surfactant lavage), revealed values increased to an average of 5.3 ml/kg at 30 cm H₂O pressure, up from an average of 2.4 ml/kg 0.9 hours after meconium injury. At 5 hours, the average value for these 4 rabbits was 7.1 ml/kg.

Autopsies of KL₄-Surfactant-lavaged rabbits, performed between 5 and 6 hours after instillation of meconium, showed

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generalized expansion of the lungs, with patchy zones of partial atelectasis generally in the lower lobes (not shown). These atelectatic zones nevertheless contained regions of fine air expansion. Microscopically, the lungs exhibited clear, expanded alveoli, although the partially atelectatic areas revealed the presence of pink-stained alveolar fluid, containing moderate numbers of PMNs, but few red cells. The expanded alveoli contained less protein-rich fluid and strikingly fewer PMNs than the atelectatic alveoli (Table 8). Although not quantitated at the microscopic level, there appeared to be distinctly less meconium in the alveoli than in non-lavaged rabbits.

Table 8

The Effect of KL₄-Surfactant Treatment on the Development of Inflammation in Meconium-Injured Rabbits

		Meconium left in lungs (mg/kg) ^a	PMNs/ 12 HPF ^b	Protein (mg/ml)	RBCs (cells/ μ l \times 10 ³)	PMNs (cells/ μ l \times 10 ³)	MPO (units/ml)	IL-8 (ng/ml)	Inflammatory Index (units/ml)
20	KL ₄ - surfactant lavage (n=9)	122.4 \pm 4.41	132 \pm 21	3.3 \pm 0.6	7.9 \pm 2.3	7.4 \pm 1.9	1016 \pm 315	12.4 \pm 3.6	1.00 \pm 0.31
25	Saline lavag e (n=5)	100.8 \pm 9.7	595 \pm 73	4.1 \pm 0.4	22.0 \pm 4.1	4.3 \pm 1.2	1755 \pm 132	4.9 \pm 2.2	1.88 \pm 0.18
30	KL ₄ - surfactant bolus (n=5)	187.5 \pm 0	216 \pm 30	5.7 \pm 0.3	23.6 \pm 8.5	16.1 \pm 2.0	1374 \pm 145	24.3 \pm 8.2	1.98 \pm 0.24

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No treat- ment (n=5)	187.5 ± 0	431 ± 24	6.0 ± 0.9	58.3 ± 20.7	5.1 ± 1.3	1490 ± 537	37.9 ± 21.8	2.01 ± 0.58
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Note: all values represent the mean ± SEM.

^a Calculated by subtracting the amount of meconium recovered in the lavages from the amount instilled into the animal.

^b The number of polymorphonuclear cells detected histologically in 12 high power fields.

Seven rabbits receiving 2 lavages with KL₄-Surfactant (2 mg/ml) followed by a bolus of 100-150 mg (at a concentration of 30 mg/ml) showed responses in PaO₂ comparable to those of the previous KL₄-Surfactant lavage group. Compliance values and pathologic findings were also similar (data not shown).

The lungs of rabbits receiving lavage with saline, rather than KL₄-Surfactant, were totally atelectatic, except for small caps of expanded lung on the apical portions of the upper lobe (not shown). Microscopically, the alveoli were densely packed, and no air expansion was present. The alveolar spaces contained protein-rich fluid and an abundance of PMNs and red cells (Table 8). Small amounts of meconium, similar to those seen in surfactant-lavaged rabbits, were found.

As recorded in Table 8, analysis of bronchoalveolar lavage fluids, taken at the time of autopsy from rabbits lavaged with KL₄-Surfactant, revealed lower levels of protein, myeloperoxidase and red cells and a lower inflammatory index than fluids from rabbits not receiving lavage. These values in KL₄-Surfactant-lavaged rabbits were also lower, except for IL-8 levels, than those in saline-lavaged rabbits.

Seven additional meconium-injured rabbits received 2 lavages with KL₄-Surfactant at 2 mg/ml as above, but followed by bolus administration of KL₄-Surfactant of 100 or 150 mg/kg at 30

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mg/ml concentration. The improvement in PaO_2 , compliance and autopsy findings were similar to those in the KL_4 -Surfactant-lavage group (data not shown).

5 iii. The efficacy of treatment of meconium-injured rabbit lungs with bolus instillation of KL_4 -Surfactant (without lavage).

Five rabbits were given 187.5 mg meconium intratracheally as before, and after 1 hour, each received a 100
10 mg/kg bolus of KL_4 -Surfactant at 30 mg/ml. The results are shown in Figure 7.

There was a moderate rise in PaO_2 from 56 mm Hg to approximately 200 mm Hg between 1 and 2 hours after instillation of the KL_4 -Surfactant. After this time period, however, the PaO_2
15 gradually subsided, falling below 100 mm Hg by 3 hours after treatment. Compliance values at 5.1 hours after meconium injury were nearly the same as those 0.9 hours after meconium injury, i.e., before treatment with KL_4 -Surfactant bolus (Table 6). At
20 autopsy, the lungs were almost completely collapsed, except for the small caps of uninvolved, expanded lung on the apices of the upper lobes that were apparently not exposed to meconium (not shown). Microscopically, approximately 80% of alveoli were filled with proteinaceous fluid and leukocytes (Table 8), and abundant meconium, but with scattered groups of alveoli showing
25 expansion. Analysis of terminal bronchoalveolar lavage fluid revealed a marked inflammatory response (Table 8).

Therefore, measurements of the efficacy of treatment with KL_4 -Surfactant by lavage as opposed to bolus instillation revealed that the method of lavage was superior both from the
30 standpoint of improved gas exchange, and also the lessened inflammatory response. The data showed that while bolus instillation, without lavage, resulted in a modest increase in

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PaO₂ over the first two hours, the effect was ephemeral, with PaO₂ values returning to levels at or below 100 mm Hg within about 2 hours. This transient effect may be explained by the continued presence of meconium in the lungs which may have
5 directly inactivated the instilled KL₄-Surfactant (and native surfactant) in the lung. Additionally, bolus treatment with KL₄-Surfactant failed to reduce the inflammatory response to meconium at 3-5 hours, allowing the inflammation to inactivate further the surfactant and also impede pulmonary function
10 independently of its action on surfactant.

c. Primate Lavage Model and Instillation Protocol

In this model, newborn rhesus monkeys, after receiving human meconium intratracheally before their first breath,
15 developed severe loss of pulmonary function. Treatment of these monkeys 1-5 hours after birth with BAL including lavage with dilute KL₄-Surfactant, produced clearing of chest radiographs and a rapid improvement in pulmonary function, with a/A ratios rising into the normal range, where they remained through the
20 study period.

The primate studies were limited to 10 newborn rhesus monkeys. Rhesus monkeys were delivered by Cesarean section at the time of full-term gestation (157-160 days), performed by the veterinary staff of the Primate Center of the University of
25 California, Davis. After delivery of the head and neck, vecuronium bromide was injected IM, and tracheotomy was performed with placement of a 2.0 mm internal diameter endotracheal tube with the distal tip being 0.5 to 1 cm above the carina prior to delivery of the body and clamping of the
30 umbilical cord. The endotracheal tube was clamped to prevent gasping, and delivery was completed.

Each newborn rhesus was weighed and placed under a radiant

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warmer and meconium was instilled through the endotracheal tube, into the fluid-filled lungs prior to the first breath. Each animal was then placed on a mechanical ventilator set on IMV: FiO_2 of 0.8-1.0, PIP of 30-35 cm H_2O , PEEP of 4 cm H_2O , and 40
5 breaths/min with inspiratory time of 0.4 s.

A 3.5 French umbilical artery catheter was inserted into the aorta (to L4) to obtain arterial blood samples and for administration of fluids. The monkey received 5-8.3 ml/kg/hr of 5% dextrose in water with 0.5 U/ml heparin throughout the study.

10 Continuous measurements of heart rate, arterial blood pressure, arterial blood oxygen saturation and rectal temperature were maintained through the study. Arterial blood samples were obtained every 20-60 min for blood gas and pH analyses. Mechanical ventilation and FiO_2 were adjusted to
15 maintain PaO_2 of 50-70 mm Hg, PaCO_2 of 40-50 mm Hg and $\text{pH} > 7.25$. Chest radiographs were obtained within 1 hour of birth and meconium administration, within 1 hour of surfactant treatment and at various intervals thereafter as noted. Paralysis was maintained throughout the study with vecuronium bromide.

20 Lavage with dilute KL_4 -Surfactant was performed through a 3.5 French umbilical catheter inserted through the endotracheal tube and cut so the tip was just distal to the tip of the tube. The monkeys received 100% O_2 throughout the procedure. Lavage was performed with KL_4 -Surfactant diluted to 2 mg/ml, using 10-20
25 ml/kg, divided equally between right side and left side and administered as described for rabbits (above). Monkeys received 1-3 subsequent lavages using KL_4 -Surfactant at 2 mg/ml and either a final lavage at 15 mg/ml or a bolus of 100 mg at 30 mg/ml. Cutaneous saturation of the blood was monitored throughout the
30 procedure.

In 5 animals, a second instillation of meconium was given. Increasing doses of meconium were given: 2 monkeys receiving

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187.5 mg/kg, 5 receiving 563 mg/kg, 2 receiving 750 mg/kg, and one receiving 843.8 mg/kg (mean=553.1 mg/kg). The a/A ratio in all meconium-treated monkeys within 1 hour after instillation of the full dose of meconium fell to approximately 0.20 or less.

5 Chest radiographs showed diffuse opacity, characteristic of MAS. Noteworthy was a marked sensitivity of the monkeys to handling, with sharp decrements in oxygen saturation occurring that lasted 2-10 min. Seven of the monkeys were treated by lavage with dilute KL₄-Surfactant at times ranging from 1.6 to 5.4 hours
10 after birth and instillation of meconium. The other three monkeys served as controls and were maintained for 20-24 hours with ventilatory support. The control animal treated with the lowest dose of meconium (187.5 mg/kg), given in two doses, recovered with a rise in a/A into the normal range (>0.4) noted
15 about 2 hours after the second instillation of meconium. The dose of meconium used in this animal and in a lavage-treated animal receiving the same dose was, therefore, considered insufficient to elicit and maintain severe pulmonary deficiency over a 20-hour period; data from these two monkeys were not
20 included in the results discussed below.

Figure 8 shows the mean a/A ratio over time for the 6 monkeys receiving ≥ 563 mg/kg (mean = 656 mg/kg) of meconium and treated with lavage with dilute KL₄-Surfactant. Of the two control animals treated with a comparable amount of meconium,
25 a/A ratios were not obtainable for one due to an inability to establish an arterial line. The a/A ratio in the other control animal remained at approximately 0.1 over an 18 hour period (Figure 8). In addition, three monkeys, receiving 563, 750 and 843.8 mg meconium/kg were monitored for 2.6, 3.2 and 5.4 hours,
30 respectively, before treatment with surfactant lavage. a/A ratios remained at approximately 0.1 to 0.25 until initiation of surfactant-lavage treatment.

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In the treatment group receiving lavage with dilute KL_4 -Surfactant, an abrupt rise in a/A ratio was observed immediately following the lavage (Figure 8). The FiO_2 was maintained at 1.0 during the period of lavages with PaO_2 values after treatment typically being >300 mm Hg. This resulted in aberrantly high a/A ratios and when the FiO_2 was lowered to the point that PaO_2 was in the range of 50-70 mm Hg, the a/A ratios decreased as shown one hour after surfactant lavage in Figure 8. In a few monkeys the a/A ratio fell transiently to <0.2 even in the presence of clearing chest radiographs (see below). By approximately 4-8 hours after lavage-treatment with KL_4 -Surfactant, the a/A ratios rose into the normal range. All treated animals were breathing room air by the termination of the study period (mean time to $FiO_2 = 0.21$ was 11.2 hours).

An appreciable clearing of the chest radiographs could be seen within 30 min after the start of surfactant lavage (not shown). Nearly complete clearing was observed within 18-20 hours. Generalized opacity of the chest radiographs remained in the two control animals over the 18 hour period with some evidence of peripheral clearing after approximately 10 hours.

At 18-24 hours of age, the animals were euthanized. Gross inspection of the meconium-injured lungs of monkeys that were lavaged with KL_4 -Surfactant revealed generalized expansion, with scattered small zones of dark red atelectasis, mostly in the dorsal (dependent) regions of the lower lobes. Cut sections of these atelectatic zones showed that they involved 1-2 mm of the surface, with light-pink, expanded lung beneath. By contrast, lungs of the two monkeys receiving meconium, but without KL_4 -Surfactant treatment, were $>80\%$ atelectatic. Microscopically, the lungs of monkeys treated with KL_4 -Surfactant-lavage were expanded with clear alveoli and a small amount of meconium, edema and leukocytes. In the zones of atelectasis, meconium was

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present in large quantities along with PMNs and modest amounts of edema fluid. The lungs of monkeys not treated with surfactant were collapsed and filled with meconium, neutrophils and some edema. There was little to no expansion. The lobes of the lung not taken for microscopic analysis were lavaged twice with saline for analysis of the inflammatory reaction. The results of these analyses are shown in Table 9. The data show a diminution in the markers of inflammation in KL₄-Surfactant-lavaged animals.

Table 9

The Effect of KL₄-Surfactant Lavage on the
Development of Inflammation in Meconium-Injured Monkeys

	KL ₄ -Surfactant Lavage (n = 6)	No Treatment (n = 2)
Protein (mg/ml)	1.07 ± 0.2	4.4
RBCs (cells/mm ³)	2598 ± 1110	26800
PMNs (cells/mm ³)	1589 ± 445	2339
MPO (units/ml)	252 ± 54	1099
IL-8 (ng/ml)	1.35 ± 0.5	6.8
Inflammatory Index (units/ml)	0.17 ± 0.5	2.6

Note: values for the animals receiving KL₄-Surfactant are the mean ± SEM for the 6 treated animals; because n = 2 in the control group, SEM was not calculated.

d. The effect of lavage treatment of meconium-injured lungs using KL₄-Surfactant

The data in this study indicate that in models of meconium aspiration syndrome (MAS) in rabbit and newborn monkeys pulmonary function can be greatly improved within minutes by lavage of the lungs with dilute KL₄-Surfactant followed by

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instillation of a sustaining dose. PaO_2 , a/A ratio, pulmonary compliance and chest radiographs all revealed rapid improvement.

Two species were employed: adult rabbits that exhibit a brisk and marked inflammatory response to instillation of human
5 meconium; and newborn primates (*Macaca mulatta*) that were given human meconium intratracheally in the amniotic fluid of the lung at the time of Cesarean delivery and before the first breath.

The primate model mimics closely the situation in human infants who aspirate meconium in utero shortly before birth. Of
10 particular interest, the improvement in pulmonary function in rhesus monkeys persisted and the clearing of chest radiographs continued over the course of the study, approximately 20 hours. The monkeys were breathing room air at approximately 11 hours after receiving KL_4 -Surfactant lavage.

15 In both rabbits and rhesus monkeys, the instilled meconium induced a rapid fall in gas exchange (Figures 3, 8) and lung compliance (Figures 4A-4D) associated with the development of atelectasis.

Three mechanisms have been proposed to explain the
20 meconium-induced decrement in pulmonary function: 1) particles of meconium may obstruct small bronchioles in the lung; 2) meconium may inhibit surfactant directly; and 3) meconium-induced inflammation may serve to inhibit surfactant. The current studies support the theory that meconium-induced
25 dysfunction of surfactant is a major factor in the loss of pulmonary function in MAS. The decrement in lung function in rabbits was associated with a loss of surfactant activity as evidenced by atelectasis associated with dysfunction of surfactant removed from the lung (Table 7). These data are
30 consistent with previous in vitro data showing that mixing meconium, or organic and aqueous extracts of meconium with surfactant leads to surfactant dysfunction. The mechanism of

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the inactivation and the constituents of the meconium responsible remain unknown. By contrast, loss of pulmonary function owing to particulate meconium appears unlikely in the present study, given that the meconium was filtered, plugs were
5 not observed microscopically in bronchi and lavage with saline alone failed to expand the alveoli and improve lung function.

The present data indicate that lavage with dilute KL₄-Surfactant removed sufficient amounts of meconium in both rabbits and monkeys to allow the KL₄-Surfactant, possibly coupled
10 with residual native surfactant, to expand the alveoli, improve pulmonary function and compliance and diminish the development of inflammation. Newborn rhesus monkeys, after receiving human meconium intratracheally before their first breath, developed severe loss of pulmonary function. Treatment of these monkeys
15 1-5 hours after birth with BAL including lavage with dilute KL₄-Surfactant, produced clearing of chest radiographs and a rapid improvement in pulmonary function, with a/A ratios rising into the normal range, where they remained through the study period.

In contrast, lavage of the lungs with saline, rather than
20 surfactant, failed to improve pulmonary function and, in fact, resulted in a greater inflammatory reaction in the lung. The detrimental effect of saline lavage or bolus instillation of saline has been reported.

25 e. The effect of KL₄-Surfactant lavage on the development of inflammation in meconium-injured lungs

The amount of pulmonary inflammation in meconium-injured adult rabbits was compared in four treatment groups: KL₄-Surfactant-lavaged rabbits, saline-lavaged rabbits, rabbits
30 treated with KL₄-Surfactant by bolus instillation, and rabbits receiving meconium alone (Table 8). The data indicate that meconium-injured rabbits receiving lavage treatment with KL₄-

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Surfactant exhibited less pulmonary inflammation than untreated controls, saline-lavaged rabbits or bolus-surfactant-treated rabbits. This was observed both in the terminal lavage fluids and microscopic sections of the lungs. The diminution of inflammation was striking in microscopic sections of lung of KL₄-Surfactant-lavaged rabbits in which small zones of atelectasis contained abundant edema and PMNs and RBCs, while the neighboring expanded lung was nearly devoid of each. Comparison of the amount of inflammation in the surfactant-lavaged and saline-lavaged rabbits suggests that the KL₄-Surfactant lavage reduced the inflammatory reaction even though nearly equal amounts of residual meconium were present in lungs in the two groups.

The mechanism of the inhibitory effect on inflammation by surfactant is unclear. One possible explanation is that surfactants, including KL₄-Surfactant, have been found to inhibit the function of inflammatory cells, which may diminish their contribution to the inflammatory reaction. (See Hayakawa et al, Am. Rev. Respir. Dis., 140:1390-1397, 1989; Geertsma et al, J. Immunol., 150:2391-2400, 1993; Suzuki et al, Am. Rev. Respir. Dis., 145:A876 (Abstr.), 1992; Yoshida et al, Life Sci., 49:1359-1365, 1991; Chao et al, J. Clin. Invest., 96:2654-2660, 1995; and Ahuja et al, Am. J. Respir. Cell. Mol. Biol., 14:496-503, 1996). Similarly, expansion of the alveoli and restoration of lung function by the KL₄-Surfactant lavage may diminish the formation of edema, thus reducing the amount of potential substrate for mediators of inflammation.

6. Premature Infant Rhesus Monkey Model for Evaluating Surfactant Activity

A preterm infant monkey model was also used to evaluate the efficacy of surfactants to treat lung function deficiencies.

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Rhesus monkeys (Macaca mulatta) were delivered by cesarian section at 127-131 days gestation, and are known to be deficient in natural pulmonary surfactant. The monkeys were prepared as described in Example 5 for tracheotomy, connected to a ventilator and maintained with mechanical ventilation as described.

Respiratory distress was then diagnosed by observing clinical and radiographic criteria of a ratio of arterial to alveolar oxygen tension (a/A) of less than 0.22 and diffuse granular pulmonary radiopacity on chest radiographs. Thereafter, each monkey was dosed with a test composition intratracheally through the umbilical catheter in the endotracheal tube in which one half of the dose was administered with the animal in the right lateral decubitus position and half in the left lateral decubitus position and with the ventilation transiently paused for about 10-30 seconds for dose instillation.

KL₄-Surfactant prepared as described in Example 4 was instilled at about 5.0 to 5.7 ml per kg. A non-peptide containing surfactant, Exosurf Neonatal (Burroghs Wellcome Co., Research Triangle Park, NC) was reconstituted with water to contain per ml: 13.5 mg DPPC, 1.5 mg cetyl alcohol and 1.0 mg tyloxapol in 0.1 N NaCl, and instilled at the dosage of 5.0 ml per kg. Thirty monkeys received KL₄-Surfactant at a dosage of 100 mg per kg (24 monkeys) or 99 mg per kg (6 monkeys) at a mean age of 1.45 hour, and nine monkeys received Exosurf at a mean age of 2.2 hour, and a/A lung function measurements were calculated at various times as listed in Figure 2. Lungs of monkeys receiving KL₄-Surfactant (solid bars) functioned dramatically better than lungs of monkeys treated with Exosurf (hatched bars).

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7. Use of Pulmonary Surfactant as a Lavage Agent to Remove
Inflammatory Mediators and Restore Pulmonary Function in a
Rabbit Inflammation Model

Direct instillation of lipopolysaccharide (LPS) into the
5 adult rabbit lungs was used as a model for respiratory distress
accompanied by inflammatory mediators. This model was evaluated
using the dilute surfactant lavage method.

Thirteen adult rabbits were partially depleted of intrinsic
lung surfactant and given intratracheal instillation of a bolus
10 of bacterial LPS at 0.75 micrograms (ug) per kg in a total
volume of 3 mls per kg. The rabbits were then maintained on the
ventilator apparatus as described in Example 5 for about 3 hours
to allow an inflammatory response to develop.

After 3-4 hours, six rabbits received three lavage washes
15 of 20 ml per kg were given over a 30 minute time period, with
ten minutes per cycle, using KL₄-Surfactant prepared as described
in Example 5 at 5 mg/ml. 100% O₂ was administered through the
ventilator throughout the procedure. Seven remained untreated
as controls.

20 Figure 9 illustrates the pulmonary function in rabbits
using pulmonary lavage following LPS injury. The PaO₂ levels
fall as the lungs are injured by the LPS within minutes after
LPS is instilled. Lavage with the pulmonary surfactant
composition dramatically improved lung function and PaO₂ levels,
25 whereas untreated controls did not show improvement of lung
function.

To determine the effect on inflammatory components in the
present LPS-injury model, the lavage wash was collected from the
rabbits in each of the above three wash cycles and the collected
30 wash was evaluated for the presence of components for the
inflammatory process by measuring total protein,
myeloperoxidase, polymorphonuclear cells (PMN's) and

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erythrocytes, as described in Example 5. As shown in Figure 10, the levels of all four components progressively decreased with each successive lavage indicating that the lavage method was effective at removing components of inflammation.

5 To evaluate the long term effect of the dilute surfactant lavage therapy on pulmonary inflammation, the same rabbits were also analyzed for the content of inflammatory components about four hours after the treatment. To that end, rabbits were monitored for about 3.5 hours after the beginning of the
10 surfactant lavage and it was observed that the PaO₂ levels did not improve with the control rabbits, but the levels did improve for the surfactant lavaged animals. Thereafter, the animals were sacrificed, the lungs were recovered and the lower lung lobe was washed ex vivo by adding 10 mls of normal saline to one
15 lobe and aspirating the wash to collect alveolar contents. The aspirated wash was assayed as described for Figure 10, and the results are shown in Figure 11. The reduction in inflammatory components was long-term, i.e., the wash was effective at reducing the ongoing inflammatory response because there was
20 little return of the inflammatory reaction 3.5 hours after treatment with KL₄-Surfactant.

These results indicate that various inflammatory components and mediators are removed using a dilute surfactant lavage according to the present invention, and that the treatment
25 reduces ongoing inflammation. Thus, the invention can be used in any condition of respiratory distress involving inflammatory mediators present in the form of protein, enzymes, cells and the like mediators.

30 8. Porcine Lavage Model and Instillation Protocol

Piglets were also evaluated as a model for repair of pulmonary function following meconium aspiration.

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Four-day old piglets were obtained, and attached to mechanical ventilators as described in Example 7. Human meconium prepared as described in Example 5 was administered in three bolus installations over 1 hour, each bolus containing 30% (w/v) meconium and administered in a dose of 3 ml per kg. FiO_2 was maintained at 1.0 and continuously applied throughout the procedure. PEEP was maintained at 6 cm water in one group of piglets throughout (Figure 12B) and in a second group of piglets, the PEEP was maintained at 6 cm water during meconium instillation, but was increased to 8 cm water 30 minutes before the first dilute surfactant lavage, and maintained at 8 cm water for about 2 hours after the last lavage (Figure 12A). PaO_2 was monitored throughout the procedure, and the results are shown as PaO_2 over time (Figure 12). Dilute surfactant lavage used was KL_4 -Surfactant prepared as described in Example 7, and administered at 8 ml per kg per instillation in a series of installations at dosages as follows: first instillation (arrows, 1A and 1B) at 2.5 mg/ml; second instillation for Figure 12B (arrows, 2A and 2B) at 2.5 mg/ml; second instillation for Figure 12A (arrows, 2A and 2B) at 10 mg/ml; and third instillation for Figure 12B (arrows, 3A and 3B) 10 mg/ml, where the timing of the installations is indicated by the position of the arrows in the Figures, and A indicates instillation into either the piglet's right or left lung, and B indicates instillation into the piglet's other lung. Removal of pulmonary fluid after each lavage was accomplished by two or more suction using timed short (10 second) bursts of negative pressure (80 mm Hg) suction separated by one to five minute periods without suction to allow for equilibration of the PaO_2 .

The use of elevated PEEP at 8 cm water produced a striking increase in the rate of recovery of arterial oxygen following dilute surfactant lavage in the meconium-injured lung model.

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Whereas, the use of 6 cm water PEEP in combination with the lavage washes produced a slow but gradual increase in PaO_2 , the use of 8 cm water PEEP produced a rapid and greater increase in PaO_2 , indicating a quicker recovery from meconium-induced
5 respiratory distress.

These same piglets were also monitored for peripheral blood oxygen saturation using a pulsating oxymeter. As seen in Figure 13, the piglet receiving lavages with 8 cm PEEP maintained healthy levels of peripheral oxygen, whereas the piglet
10 receiving lavages with 6 cm PEEP experienced dramatic drops in the levels of peripheral oxygen.

To further characterize the preferred dilute lavage procedure in cases of respiratory distress, the duration of
15 suction for removal of the pulmonary fluids following lavage installations was evaluated. In the same piglet model, piglets were fitted with a ventilator apparatus as described and were similarly treated with meconium. FiO_2 was maintained at 1.0 and PEEP was maintained at 8 cm water throughout the procedure.
20 Peripheral blood oxygen saturation was monitored using a pulsating oxymeter throughout the procedure and expressed as SaO_2 . A lavage instillation of KL_4 -Surfactant was given at 2.5 mg/ml, and a suction at 80 mm Hg negative pressure was performed to remove pulmonary fluids shortly after terminating the lavage
25 installations. Either 10 seconds (Figure 14A) or about 60 seconds (Figure 14B) of suction was applied to remove the pulmonary fluid.

The effect of suction duration on oxygen saturation in arterial blood was dramatic, indicating that extended suctioning
30 lowers blood oxygen levels. Thus, in preferred embodiments, the suction duration should be less than 30 seconds, preferably not exceed 20 seconds, and more preferably be less than 10 seconds.

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If multiple sequential suction are to be applied, they should be separated by brief recovery periods of sufficient time (20 to 20 minutes) to optimize blood oxygen levels.

The foregoing specification, including the specific
5 embodiments and examples, is intended to be illustrative of the present invention and is not to be taken as limiting. Numerous other variations and modifications can be effected without departing from the true spirit and scope of the present invention.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

5

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10

15

(ii) TITLE OF INVENTION: NOVEL PULMONARY SURFACTANTS AND
THERAPEUTIC USES, INCLUDING PULMONARY LAVAGE

(iii) NUMBER OF SEQUENCES: 13

20

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.25

25

(v) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER: US
- (B) FILING DATE: 29-JAN-1998

30

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- (A) APPLICATION NUMBER: US 08/848,580
- (B) FILING DATE: 28-APR-1997

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 08/488,123
- (B) FILING DATE: 06-JUN-1995

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(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 08/419,824
- (B) FILING DATE: 11-APR-1995

- 112 -

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(A) APPLICATION NUMBER: US 08/060,833

(B) FILING DATE: 12-MAY-1993

(vii) PRIOR APPLICATION DATA:

5 (A) APPLICATION NUMBER: US 07/715,397

(B) FILING DATE: 14-JUN-1991

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/293,201

(B) FILING DATE: 04-JAN-1989

10 (vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/141,200

(B) FILING DATE: 06-JAN-1988

(2) INFORMATION FOR SEQ ID NO:1:

15 (I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Lys Leu Leu Leu Leu Lys Leu Leu Leu Leu Lys Leu Leu Leu Leu Lys

1 5 10 15

Leu Leu Leu Leu Lys

20

25

(2) INFORMATION FOR SEQ ID NO:2:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Leu Leu Leu Leu Leu Leu Leu Lys Leu Leu Leu Leu Leu Leu

1 5 10 15

35 Leu Leu Lys Leu Leu

20

- 113 -

(2) INFORMATION FOR SEQ ID NO:3:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Lys Lys Leu Leu Leu Leu Leu Leu Lys Lys Leu Leu Leu Leu Leu
1 5 10 15
10 Leu Leu Lys Lys Leu
20

(2) INFORMATION FOR SEQ ID NO:4:

(I) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Asp Leu Leu Leu Leu Asp Leu Leu Leu Leu Asp Leu Leu Leu Leu Asp
1 5 10 15
20 Leu Leu Leu Leu Asp
20

25 (2) INFORMATION FOR SEQ ID NO:5:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Arg Leu Leu Leu Leu Arg Leu Leu Leu Leu Arg Leu Leu Leu Leu Arg
1 5 10 15
35 Leu Leu Leu Leu Arg
20

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(2) INFORMATION FOR SEQ ID NO:6:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Arg Leu Leu Leu Leu Leu Leu Leu Arg Leu Leu Leu Leu Leu
1 5 10 15
10 Leu Leu Arg Leu Leu
20

(2) INFORMATION FOR SEQ ID NO:7:

(I) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Arg Arg Leu Leu Leu Leu Leu Leu Arg Arg Leu Leu Leu Leu
1 5 10 15
20 Leu Leu Arg Arg Leu
20

25 (2) INFORMATION FOR SEQ ID NO:8:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Arg Leu Leu Leu Leu Cys Leu Leu Leu Arg Leu Leu Leu Cys Leu
1 5 10 15
35 Leu Leu Arg

(2) INFORMATION FOR SEQ ID NO:9:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

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(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

5 Arg Leu Leu Leu Leu Cys Leu Leu Leu Arg Leu Leu Leu Cys Leu
 1 5 10 15
 Leu Leu Arg Leu Leu
 20

10 (2) INFORMATION FOR SEQ ID NO:10:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Arg Leu Leu Leu Leu Cys Leu Leu Leu Arg Leu Leu Leu Cys Leu
 1 5 10 15
 Leu Leu Arg Leu Leu Leu Cys Leu Leu Leu Arg
 20 20 25

(2) INFORMATION FOR SEQ ID NO:11:

(I) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 750 base pairs

25 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

30 (A) NAME/KEY: sig_peptide

(B) LOCATION: 1..186

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 187..729

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CACCTGGGCC TGTGCAATC CCGGCAGCCA GAGCCAGAGC AGGAGCCAGG GATGTCAGAC 60
 CCCCTGCCCA AACCTCTGCG GGACCCTCTG CCAGACCCTC TGCTGGACAA GCTCGTCGTC 120
 CCTGTGCTGC CCGGGGCCCT CCAGGCGAGG CCTGGGCCTC ACACACAGGA TCTCTCCGAG 180

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CAGCAA TTC CCC ATT CCT CTC CCC TAT TGC TGG CTC TGC AGG GCT CTG 228
 Phe Pro Ile Pro Leu Pro Tyr Cys Trp Leu Cys Arg Ala Leu
 1 5 10
 ATC AAG CGG ATC CAA GCC ATG ATT CCC AAG GGT GCG CTA GCT GTG GCA 276
 5 Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly Ala Leu Ala Val Ala
 15 20 25 30
 GTG GCC CAG GTG TGC CGC GTG GTA CCT CTG GTG GCG GGC GGC ATC TGC 324
 Val Ala Gln Val Cys Arg Val Val Pro Leu Val Ala Gly Gly Ile Cys
 35 40 45
 10 CAG TGC CTG GCT GAG CGC TAC TCC GTC ATC CTG CTC GAC ACG CTG CTG 372
 Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu Asp Thr Leu Leu
 50 55 60
 GGC CGC ATG CTG CCC CAG CTG GTC TGC CGC CTC GTC CTC CGG TGC TCC 420
 Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu Val Leu Arg Cys Ser
 15 65 70 75
 ATG GAT GAC AGC GCT GGC CCA AGG TCG CCG ACA GGA GAA TGG CTG CCG 468
 Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly Glu Trp Leu Pro
 80 85 90
 CGA GAC TCT GAG TGC CAC CTC TGC ATG TCC GTG ACC ACC CAG GCC GGG 516
 20 Arg Asp Ser Glu Cys His Leu Cys Met Ser Val Thr Thr Gln Ala Gly
 95 100 105 110
 AAC AGC AGC GAG CAG GCC ATA CCA CAG GCA ATG CTC CAG GCC TGT GTT 564
 Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met Leu Gln Ala Cys Val
 115 120 125
 25 GGC TCC TGG CTG GAC AGG GAA AAG TGC AAG CAA TTT GTG GAG CAG CAC 612
 Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe Val Glu Gln His
 130 135 140
 ACG CCC CAG CTG CTG ACC CTG GTG CCC AGG GGC TGG GAT GCC CAC ACC 660
 Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly Trp Asp Ala His Thr
 30 145 150 155
 ACC TGC CAG GCC CTC GGA GTG TGT GGG ACC ATG TCC AGC CCT CTC CAG 708
 Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met Ser Ser Pro Leu Gln
 160 165 170
 TGT ATC CAC AGC CCC GAC CTT TGATGAGAAC TCAGCTGTCC A 750
 35 Cys Ile His Ser Pro Asp Leu
 175 180

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(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 181 amino acids

(B) TYPE: amino acid

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Phe Pro Ile Pro Leu Pro Tyr Cys Trp Leu Cys Arg Ala Leu Ile Lys
 1 5 10 15
 10 Arg Ile Gln Ala Met Ile Pro Lys Gly Ala Leu Ala Val Ala Val Ala
 20 25 30
 Gln Val Cys Arg Val Val Pro Leu Val Ala Gly Gly Ile Cys Gln Cys
 35 40 45
 Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu Asp Thr Leu Leu Gly Arg
 15 50 55 60
 Met Leu Pro Gln Leu Val Cys Arg Leu Val Leu Arg Cys Ser Met Asp
 65 70 75 80
 Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly Glu Trp Leu Pro Arg Asp
 85 90 95
 20 Ser Glu Cys His Leu Cys Met Ser Val Thr Thr Gln Ala Gly Asn Ser
 100 105 110
 Ser Glu Gln Ala Ile Pro Gln Ala Met Leu Gln Ala Cys Val Gly Ser
 115 120 125
 Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe Val Glu Gln His Thr Pro
 25 130 135 140
 Gln Leu Leu Thr Leu Val Pro Arg Gly Trp Asp Ala His Thr Thr Cys
 145 150 155 160
 Gln Ala Leu Gly Val Cys Gly Thr Met Ser Ser Pro Leu Gln Cys Ile
 165 170 175
 30 His Ser Pro Asp Leu
 180

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

35 (A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

His Leu Leu Leu Leu His Leu Leu Leu Leu His Leu Leu Leu Leu His

1

5

10

15

Leu Leu Leu Leu His

5

20

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WHAT IS CLAIMED IS:

1. A method for pulmonary lavage of a mammal comprising:
 - a) applying gas positive end-expiratory pressure (PEEP) with a ventilator into a lung section of said mammal at a
5 pressure of from about 4 to 16 cm water;
 - b) instilling a lavage composition containing dilute surfactant in a pharmaceutically acceptable aqueous medium into said lung; and
 - c) removing pulmonary fluid from said lung using
10 short intervals of tracheo-bronchial suction at a negative pressure of about 20 to 100 mm mercury.
2. The method of claim 1 wherein said ventilator PEEP is applied for a preselected time period prior to instilling step (b).
- 15 3. The method of claim 2 wherein said time period is up to about 30 minutes
4. The method of claim 1 wherein said ventilator PEEP is applied continuously during steps (b) and (c)
5. The method of claim 1 wherein said ventilator PEEP is
20 applied for a preselected time period after removing step (c).
6. The method of claim 5 wherein said time period is up to about 24 hours.
7. The method of claim 6 wherein said time period is from about 0.5 to 6 hours.
- 25 8. The method of claim 1 wherein said ventilator PEEP is administered for up to about 30 minutes prior to instillation step (b), continuously throughout steps (b) and (c), and for up to about 24 hours after the completion of step (c).
9. The method of claim 1 wherein said mammal is a newborn
30 infant and wherein said ventilator PEEP levels are 4-15 cm water.
10. The method of claim 9 wherein said ventilator PEEP

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levels are 6-9 cm water.

11. The method of claim 9 wherein said ventilator PEEP levels are 8 cm water.

12. The method of claim 1 wherein said mammal is an adult,
5 a juvenile or infant.

13. The method of claim 12 wherein said ventilator PEEP levels are 6-12 cm water.

14. The method of claim 12 wherein said ventilator PEEP levels are 8-10 cm water.

10 15. The method of claim 1 wherein said gas contains 21 to 100 % oxygen.

16. The method of claim 15 wherein said gas contains 50 to 100 % oxygen.

17. The method of claim 1 wherein said dilute surfactant
15 is present in said composition at 0.1 - 50 mg per ml.

18. The method of claim 17 wherein said dilute surfactant is present in said composition at 0.5 - 20 mg per ml.

19. The method of claim 17 wherein said dilute surfactant is present in said composition at 2 - 10 mg per ml.

20 20. The method of claim 1 wherein said lavage composition is instilled in a volume of 4-60 ml per kilogram.

21. The method of claim 20 wherein said lavage composition is instilled in a volume of 8-30 ml per kilogram per lung section.

25 22. The method of claim 1 wherein said removing step interval is about 2 to 120 seconds.

23. The method of claim 22 wherein said removing step interval is about 5 to 20 seconds.

24. The method of claim 1 wherein said instilling and
30 removing steps are repeated in sequence 1 to 5 times.

25. The method of claim 1 wherein said composition is instilled in a first and second series, wherein said first

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series comprises from 1 to 3 cycles of steps (b) and (c) using dilute surfactant in said composition at 0.1 to 10 mg per ml, and wherein said second series comprises from 1 to 5 cycles of steps (b) and (c) using dilute surfactant in said composition at 5 10 to 50 mg per ml.

26. The method of claim 1 further comprising after step (c):

(d) instilling a composition containing surfactant in a pharmaceutically acceptable aqueous medium into said lung, 10 wherein said surfactant is present in said composition at 15 to 100 milligrams per ml of composition and wherein from 10 to 300 mg of surfactant is instilled per kilogram.

27. The method of claim 1 wherein said lavage is conducted to treat respiratory distress syndrome (RDS) in said mammal.

15 28. The method of claim 27 wherein said RDS is caused by meconium aspiration.

29. The method of claim 27 wherein said RDS is associated with pulmonary inflammation.

30. The method of claim 27 wherein said RDS is associated 20 with pulmonary infection.

31. The method of claim 27 wherein said RDS is associated with acute hypoxemia.

32. The method of claim 27 wherein said RDS is associated with persistant fetal circulation.

25 33. The method of claim 27 wherein said RDS is associated with congenital diaphragmatic hernia.

34. The method of claim 27 wherein said RDS is associated with sepsis, pulmonary trauma, cranial or body trauma, pancreatitis, aspiration of gastric contents, heated vapor 30 inhalation, noxious vapor inhalation, pneumonia or multiple transfusions.

35. The method of claim 1 wherein said mammal is a human.

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36. The method of claim 1 wherein said lavage composition contains a natural pulmonary surfactant isolated from a mammal, or fragment thereof.

37. The method of claim 36 wherein said mammal is selected
5 from the group consisting of bovine, porcine and human.

38. The method of claim 36 wherein said natural pulmonary surfactant is selected from the group consisting of surfactant proteins SP-B and SP-C.

39. The method of claim 36 wherein said natural pulmonary
10 surfactant is substantially isolated human pulmonary surfactant (SP) protein.

40. The method of claim 1 wherein said lavage composition comprises one or more phospholipids and is polypeptide-free.

41. The method of claim 1 wherein said surfactant is a
15 synthetic pulmonary surfactant.

42. The method of claim 41 wherein said synthetic pulmonary surfactant comprises one or more phospholipids and a polypeptide, said polypeptide, when admixed with said phospholipid, forms a synthetic pulmonary surfactant having a
20 surfactant activity greater than the surfactant activity of the phospholipid alone.

43. The method of claim 41 wherein said synthetic pulmonary surfactant comprises one or more pharmaceutically acceptable phospholipids admixed with a polypeptide comprising
25 at least 10 amino acid residues and no more than about 60 amino acid residues, said polypeptide including a sequence having alternating hydrophobic and hydrophilic amino acid residue regions represented by the formula $(Z_a U_b)_c Z_d$, wherein:

30 Z is a hydrophilic amino acid residue independently selected from the group consisting of R, D, E and K;

U is a hydrophobic amino acid residue independently selected from the group consisting of V, I, L, C and F;

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a has an average value of about 1 to about 5;
b has an average value of about 3 to about 20;
c is 1 to 10; and
d is 0 to 3.

5 44. The method of claim 43, wherein said polypeptide has
an amino acid residue sequence represented by the formula:

KLLLLKLLLLKLLLLKLLLLK.

45. The method of claim 43 wherein said polypeptide has an
amino acid residue sequence selected from the group consisting
10 of:

KLLLLKLLLLKLLLLKLLLLK,
KLLLLLLLLLKLLLLLLLLLKLL, and
KKLLLLLLLLKKLLLLLLLLKKL.

46. The method of claim 41 wherein said synthetic
15 pulmonary surfactant comprises one or more pharmaceutically
acceptable phospholipids admixed with a polypeptide having an
amino acid residue sequence selected from the group consisting
of:

20 DLLLLDLLLLDLLLLDLLLLD,
RLLLLRLLLLRLLLLRLLLLR,
RLLLLLLLLRLLLLLLLLRLL,
RLLLLLLLLRLLLLLLLLRRL,
RLLLLCLLLRLLLLCLLLR,
RLLLLCLLLRLLLLCLLLRLL, and
25 RLLLLCLLLRLLLLCLLLRLLLLCLLLR.

47. The method of claim 41 wherein said synthetic
pulmonary surfactant comprises:

- a) a polypeptide comprising at least 10 amino acid
residues and no more than about 60 amino acid residues and
30 constituted by alternating groupings of charged amino acid
residues and uncharged amino acid residues, and
b) one or more pharmaceutically acceptable

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phospholipids, wherein said polypeptide is present in an amount sufficient to increase the surfactant activity of the composition above that of said phospholipid.

48. The method of claim 42, wherein said phospholipid is present in a polypeptide:phospholipid weight ratio in the range of about 1:7 to about 1:1,000.

49. The method of claim 42, wherein said phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine
(dipalmitoylphosphatidylcholine, DPPC);
phosphatidyl glycerol (PG); and
an admixture of DPPC and PG in a weight ratio of about 3:1.

50. The method of claim 42, further comprising palmitic acid.

51. The method of claim 42 wherein said polypeptide comprises at least 10 amino acid residues and no more than about 60 amino acid residues and constituted by alternating groupings of charged amino acid residues and uncharged amino acid residues.

52. The method of claim 51 wherein said alternating groupings of amino acid residues represented by the formula $(Z_a J_b)_c Z_d$, wherein:

Z is an amino acid residue independently selected from the group consisting of R, D, E, and K;

J is an α -aminoaliphatic carboxylic acid;
a has an average value of about 1 to about 5;
b has an average value of about 3 to about 20;
c is 1 to 10; and
d is 0 to 3.

53. The method of claim 51 wherein said alternating groupings of amino acids residue regions represented by the formula $(B_a U_b)_c B_d$, wherein:

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B is an amino acid residue independently selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-hydroxyproline;

U is an amino acid residue independently selected from the
5 group consisting of V, I, L, C, Y, and F;

a has an average value of about 1 to about 5;

b has an average value of about 3 to about 20;

c is 1 to 10; and

d is 0 to 3.

10 54. The method of claim 51 wherein said alternating groupings of amino acid residues represented by the formula $(B_a J_b)_c B_d$, wherein:

B is an amino acid residue independently selected from the group consisting of H, 5-hydroxylysine, 4-hydroxyproline, and 3-
15 hydroxyproline;

J is an α -aminoaliphatic carboxylic acid;

a has an average value of about 1 to about 5;

b has an average value of about 3 to about 20;

c is 1 to 10; and

20 d is 0 to 3.

55. The method of claim 54 wherein said J is an α -aminoaliphatic carboxylic acid having four to six carbons, inclusive.

56. The method of claim 54 wherein said J is selected from
25 the group consisting of α -aminobutanoic acid, α -aminopentanoic acid, α -amino-2-methylpropanoic acid, and α -aminohexanoic acid.

57. The method of claim 42 wherein said polypeptide comprises at least 10 amino acid residues and no more than about 60 amino acid residues and constituted by alternating groupings
30 of charged amino acid residues and uncharged amino acid residues as represented by the formula $\{(\text{Charged})_a(\text{Uncharged})_b\}_c(\text{Charged})_d$, wherein:

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a has an average value of about 1 to about 5;
b has an average value of about 3 to about 20;
c is 1 to 10; and
d is 0 to 3.

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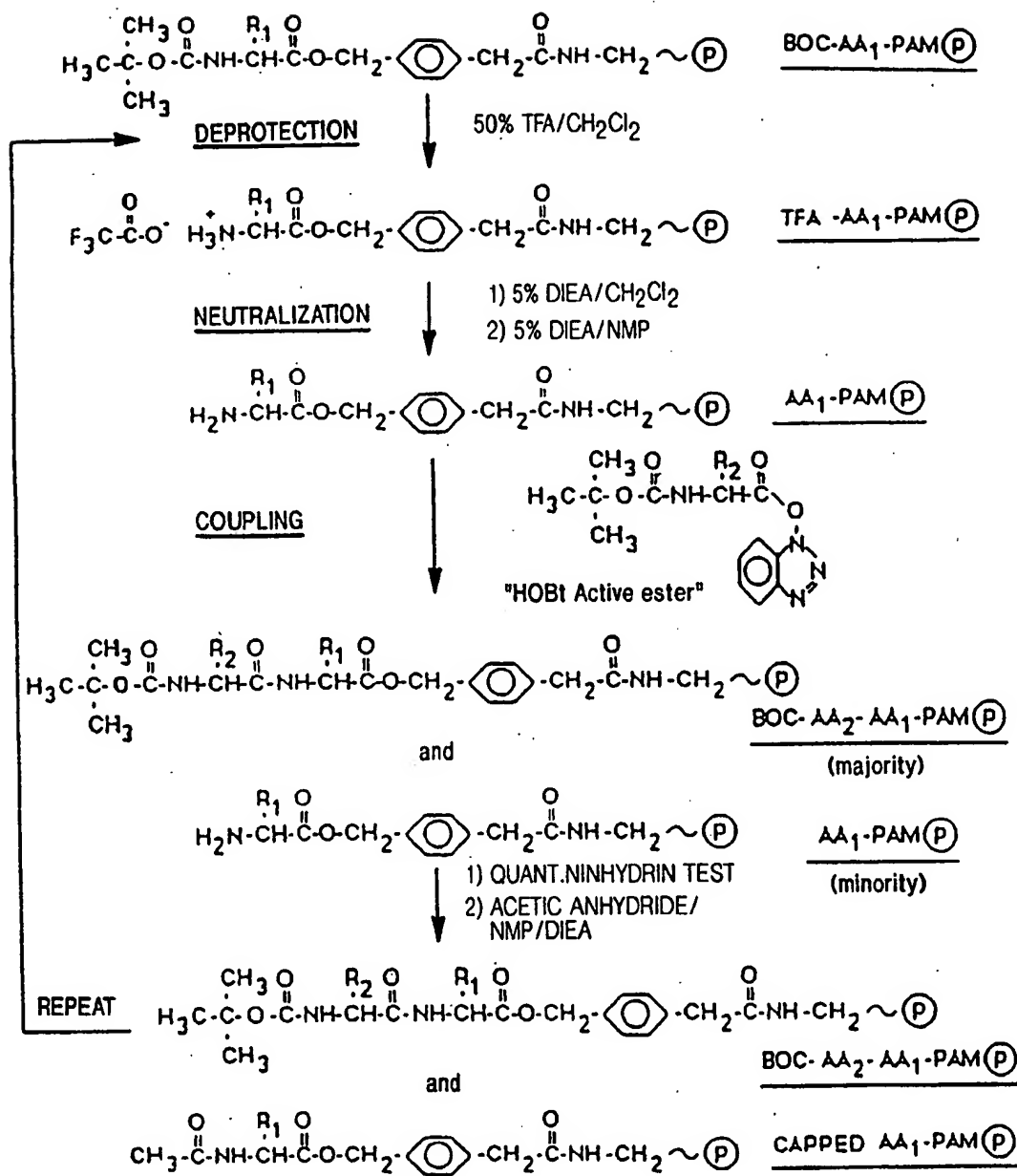


FIG. 1

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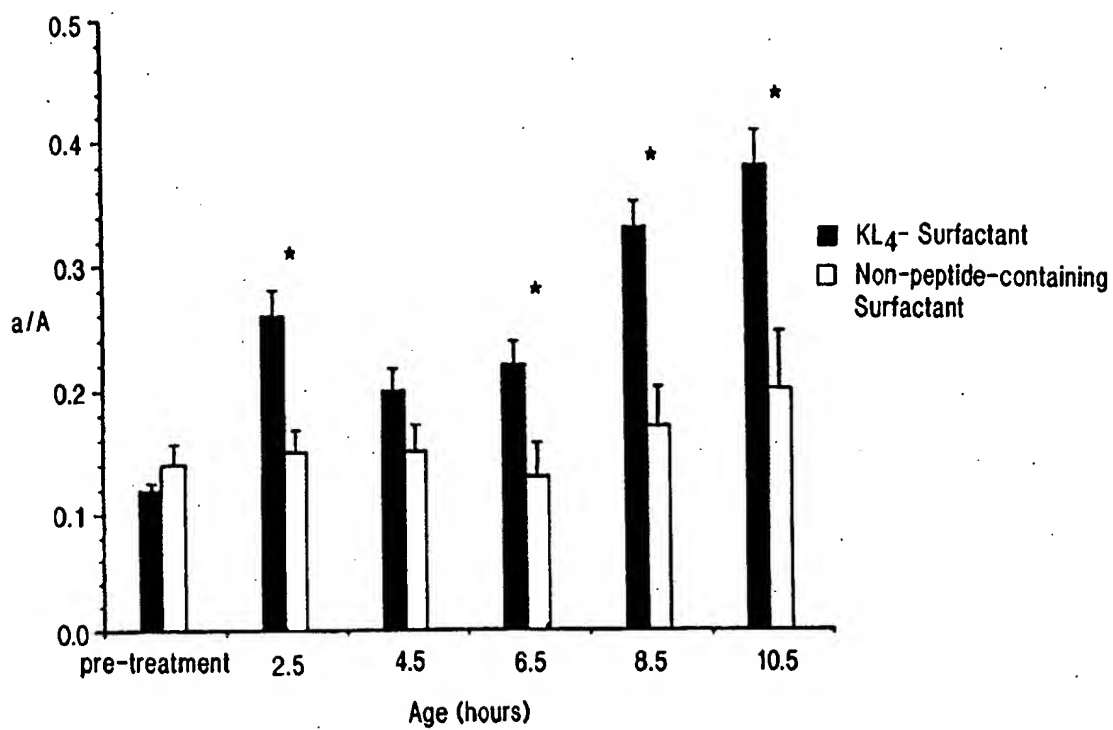


FIG. 2

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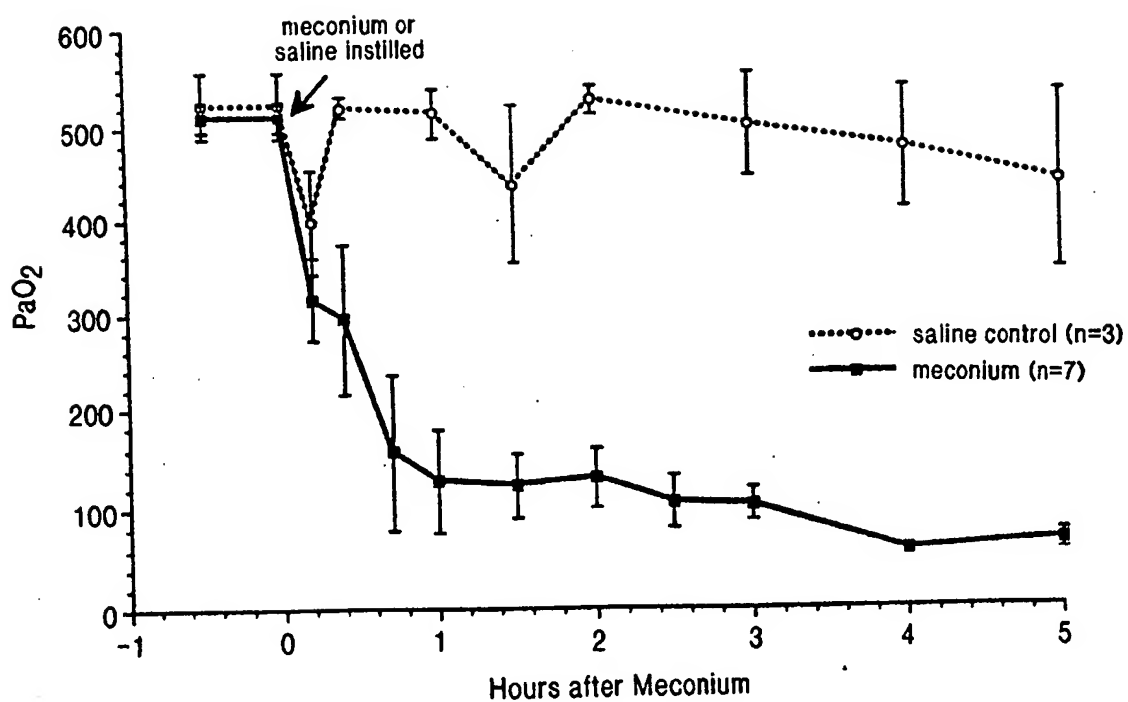


FIG. 3

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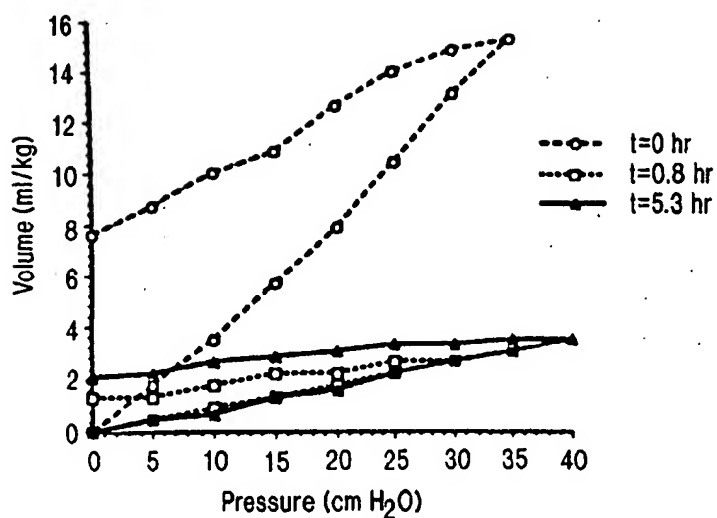


FIG. 4A

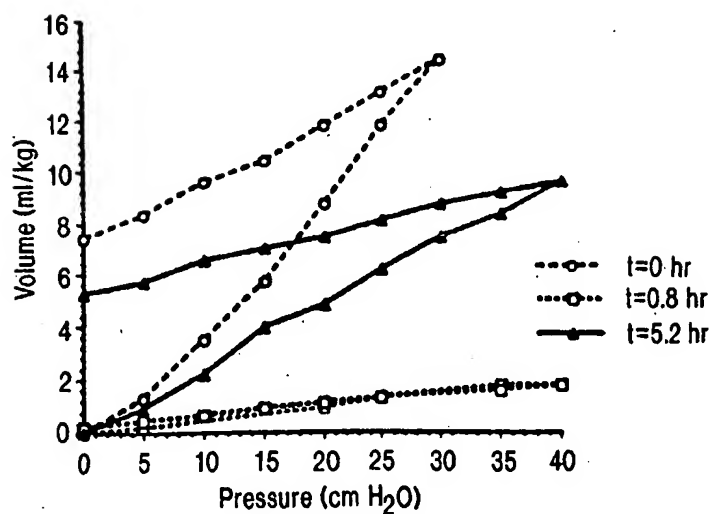


FIG. 4B

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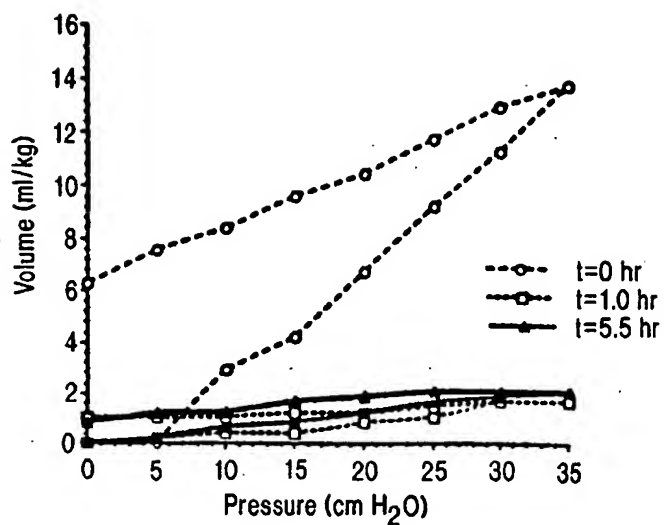


FIG. 4C

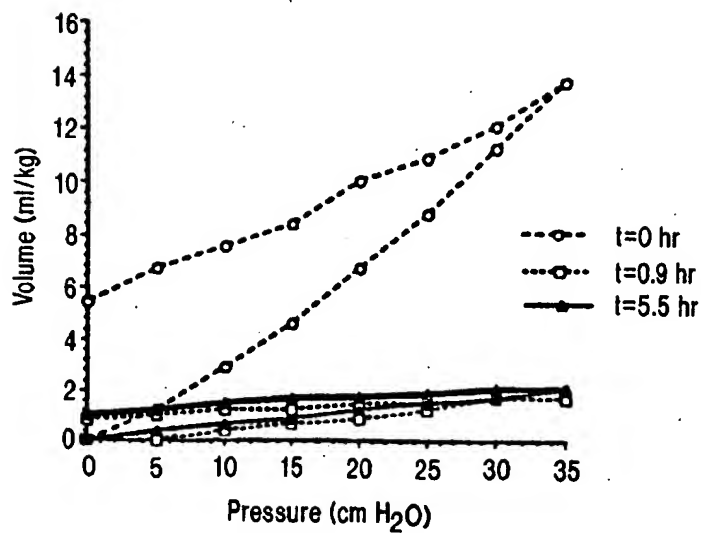
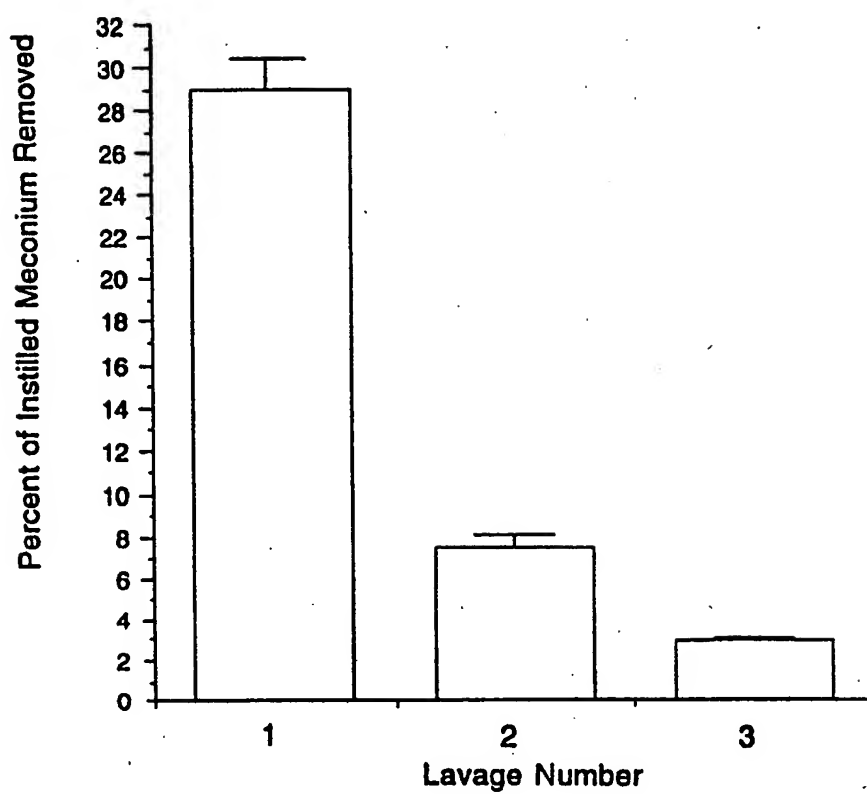


FIG. 4D

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**FIG. 5**

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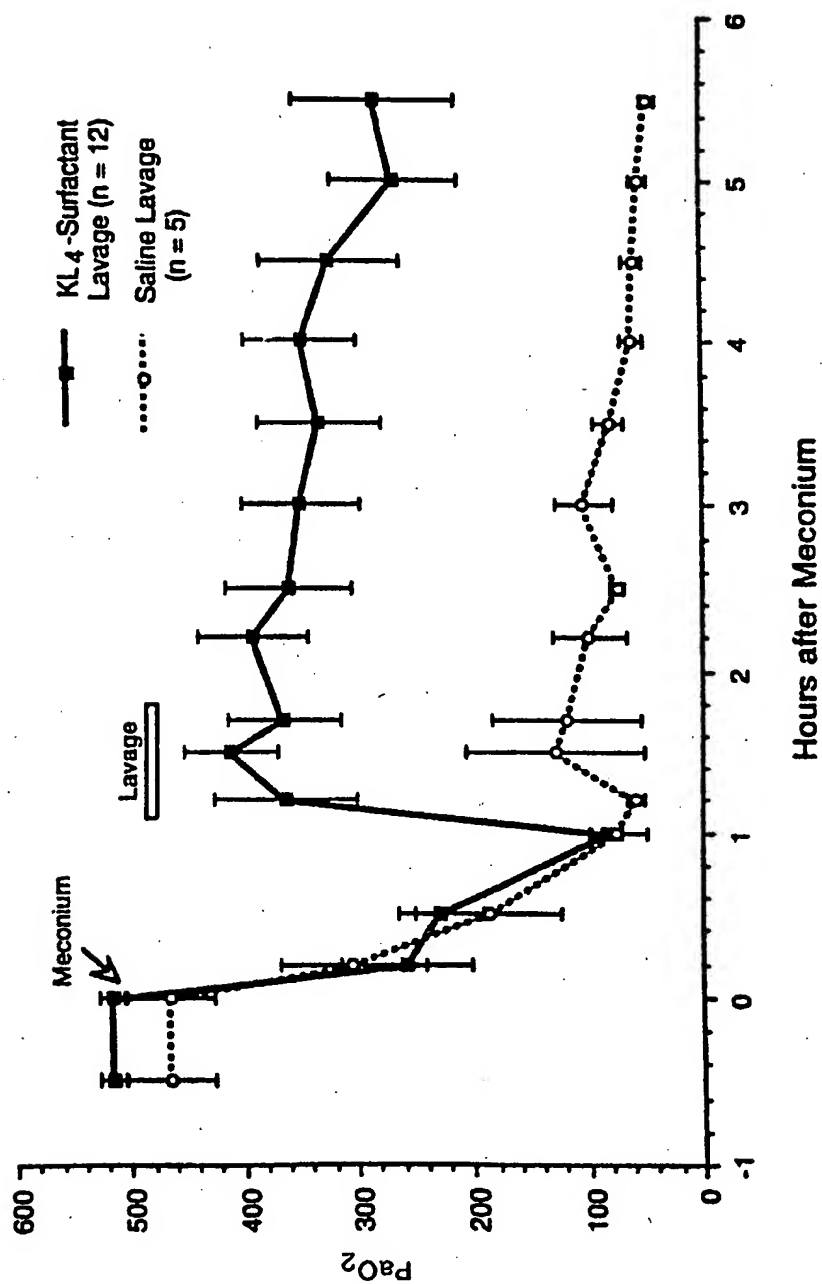


FIG. 6

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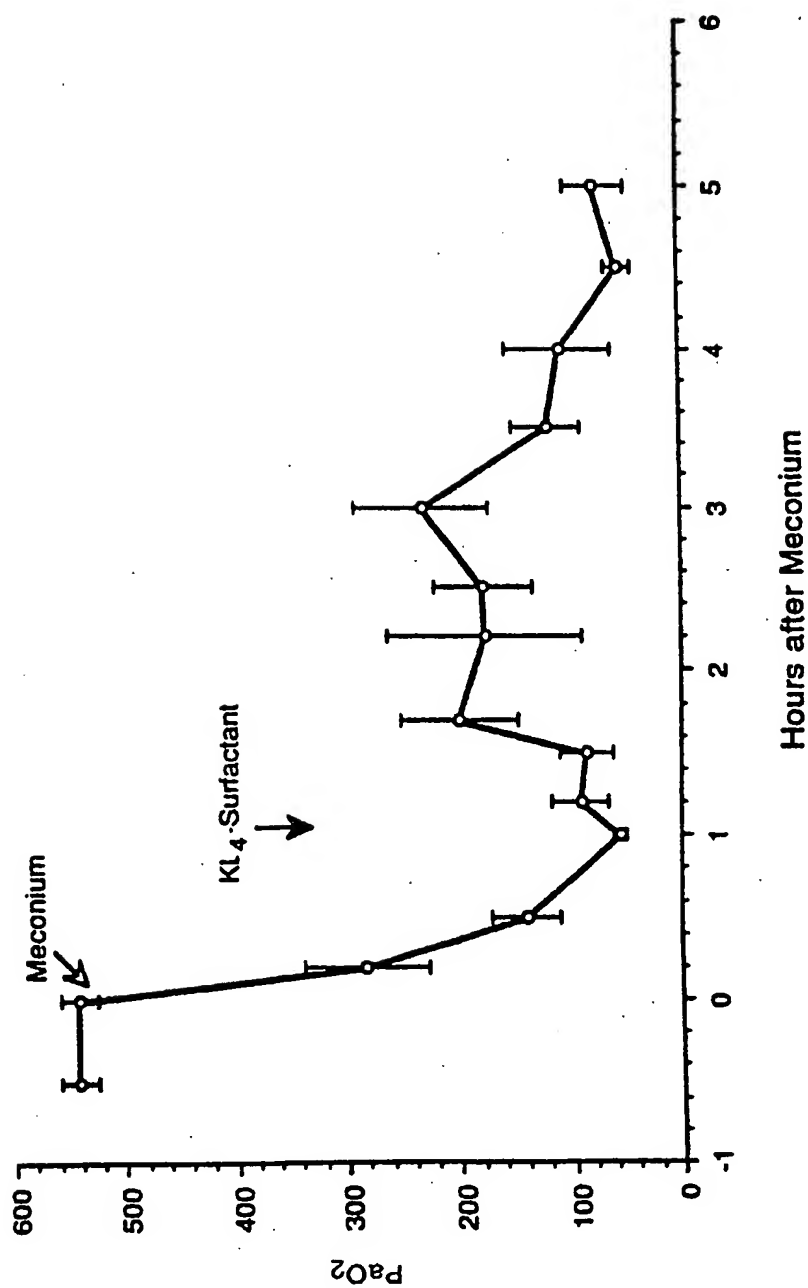


FIG. 7

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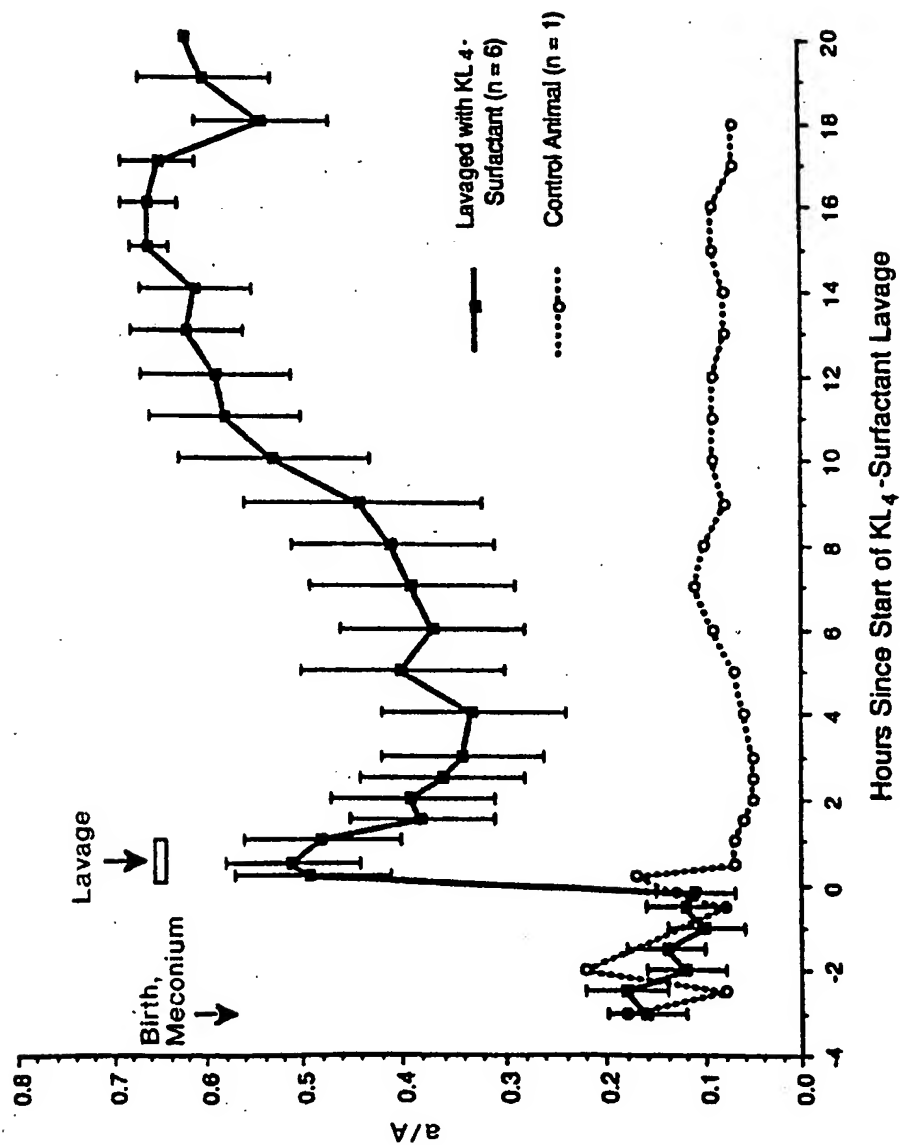


FIG. 8

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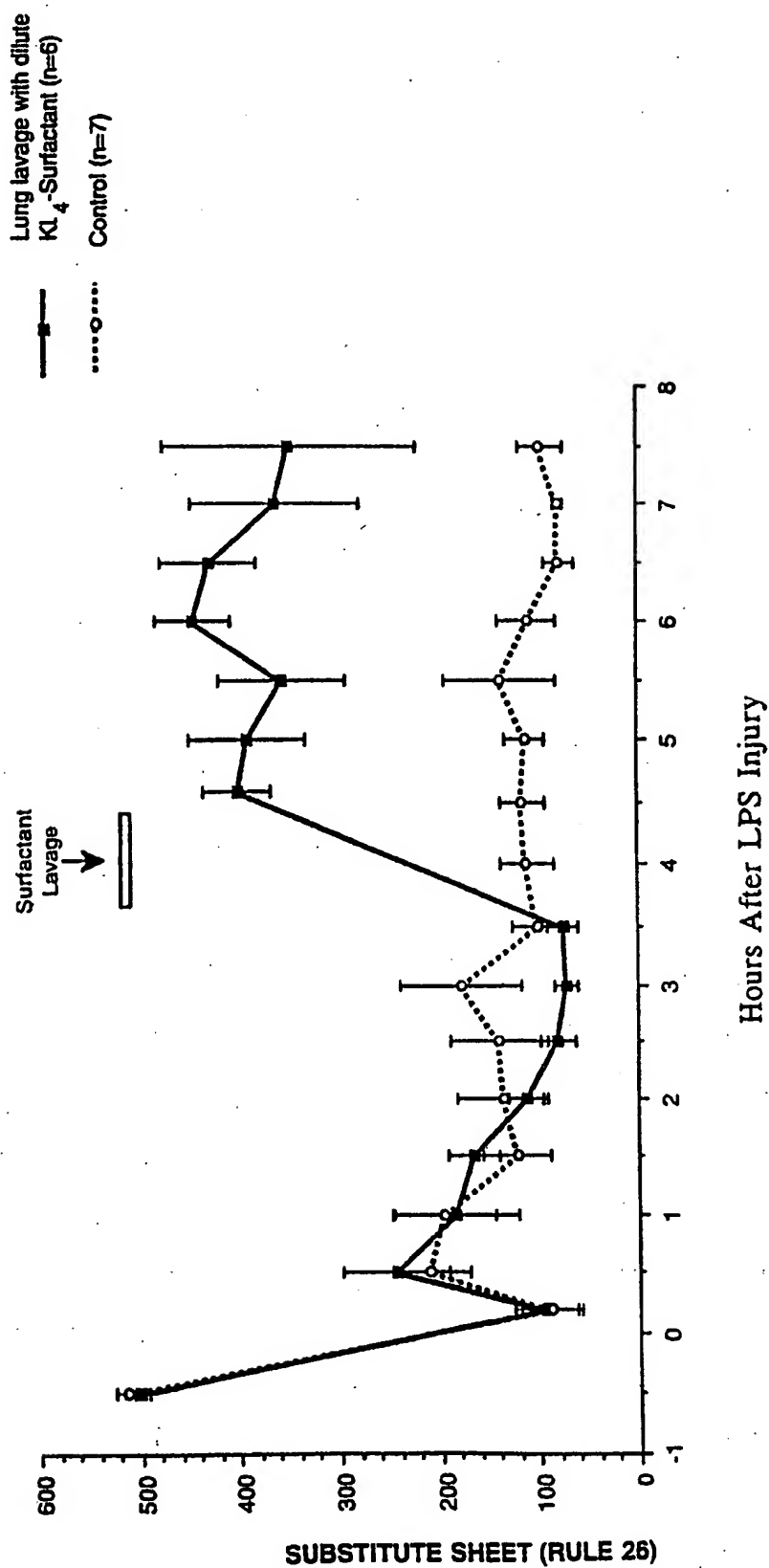


FIG. 9

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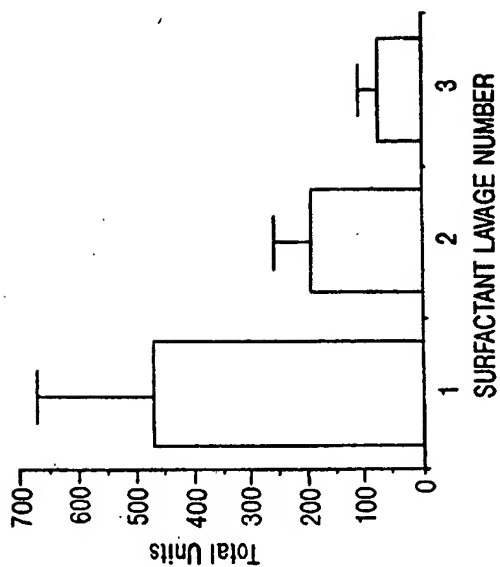


FIG. 10B

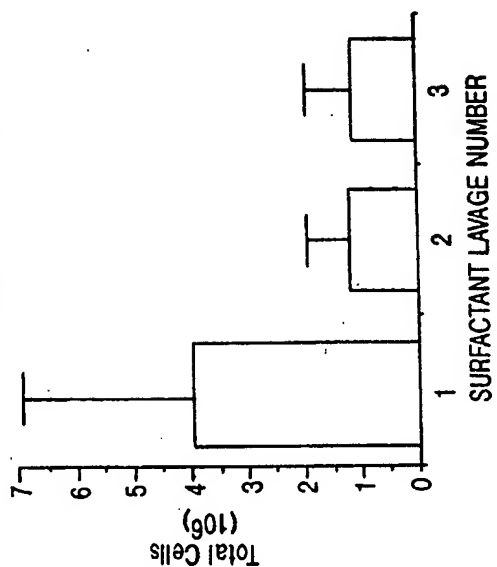


FIG. 10D

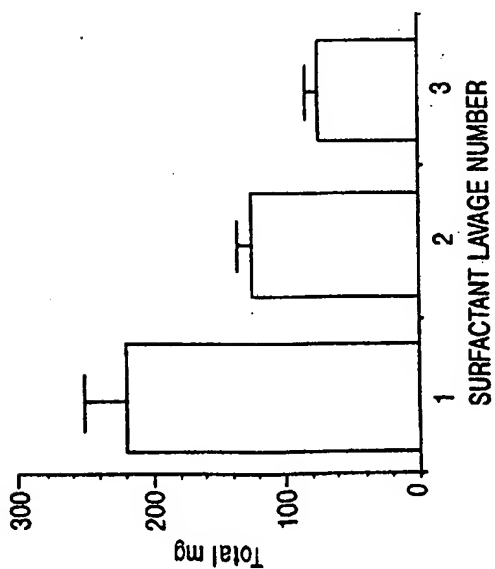


FIG. 10A

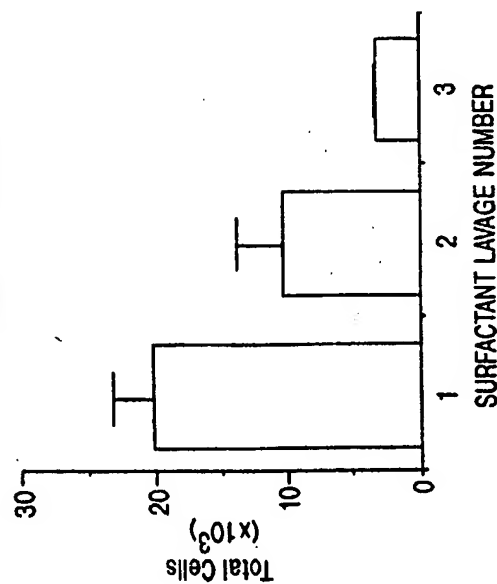


FIG. 10C

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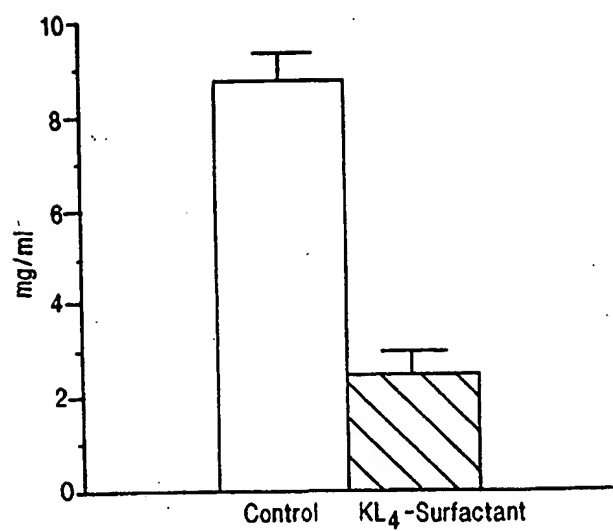


FIG. 11A

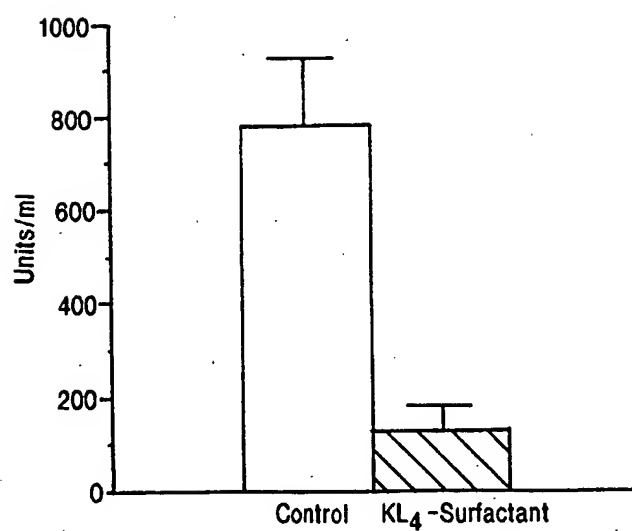


FIG. 11B

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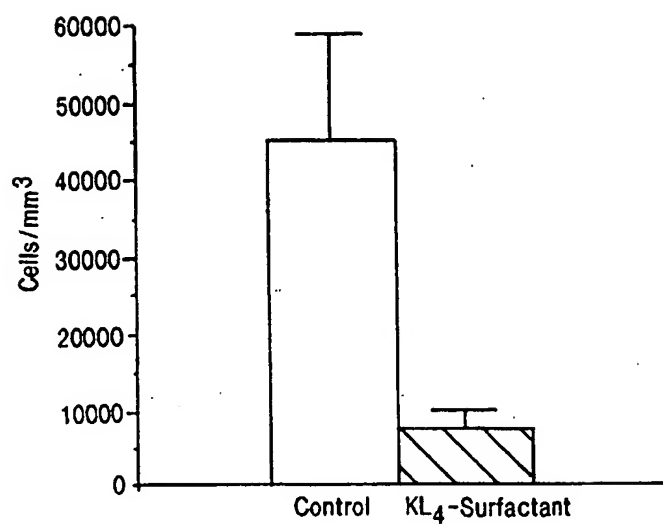


FIG. 11C

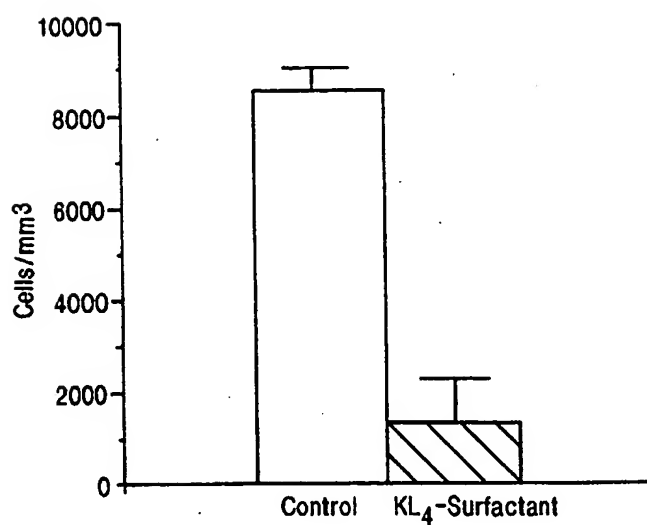


FIG. 11D

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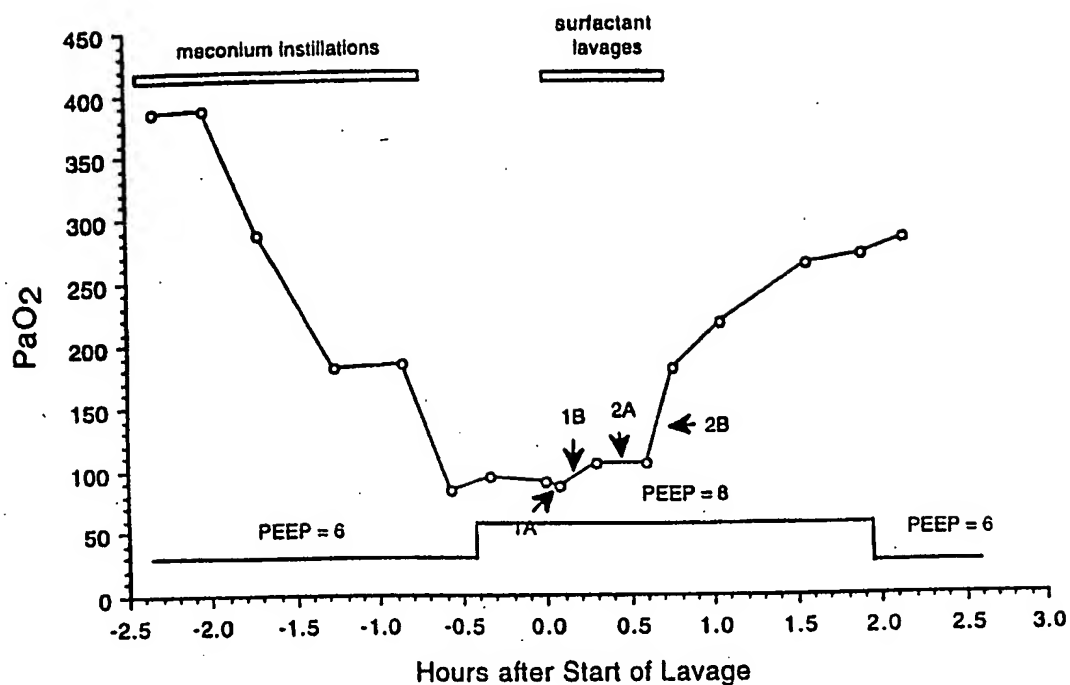


FIG. 12A

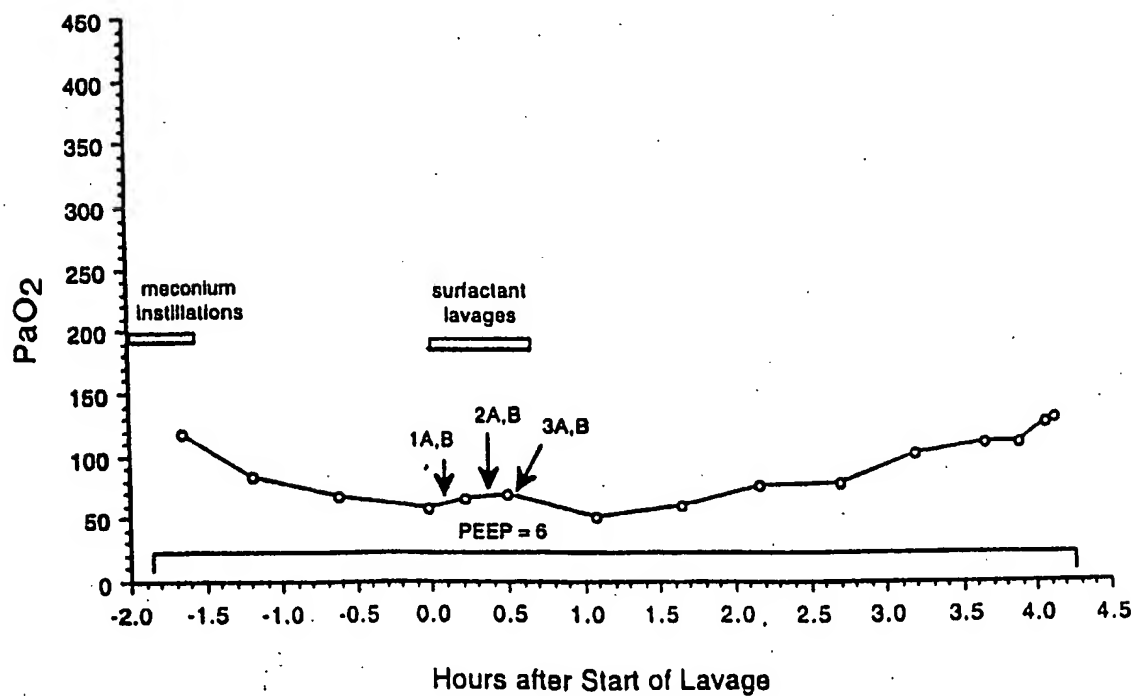


FIG. 12B

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15/16

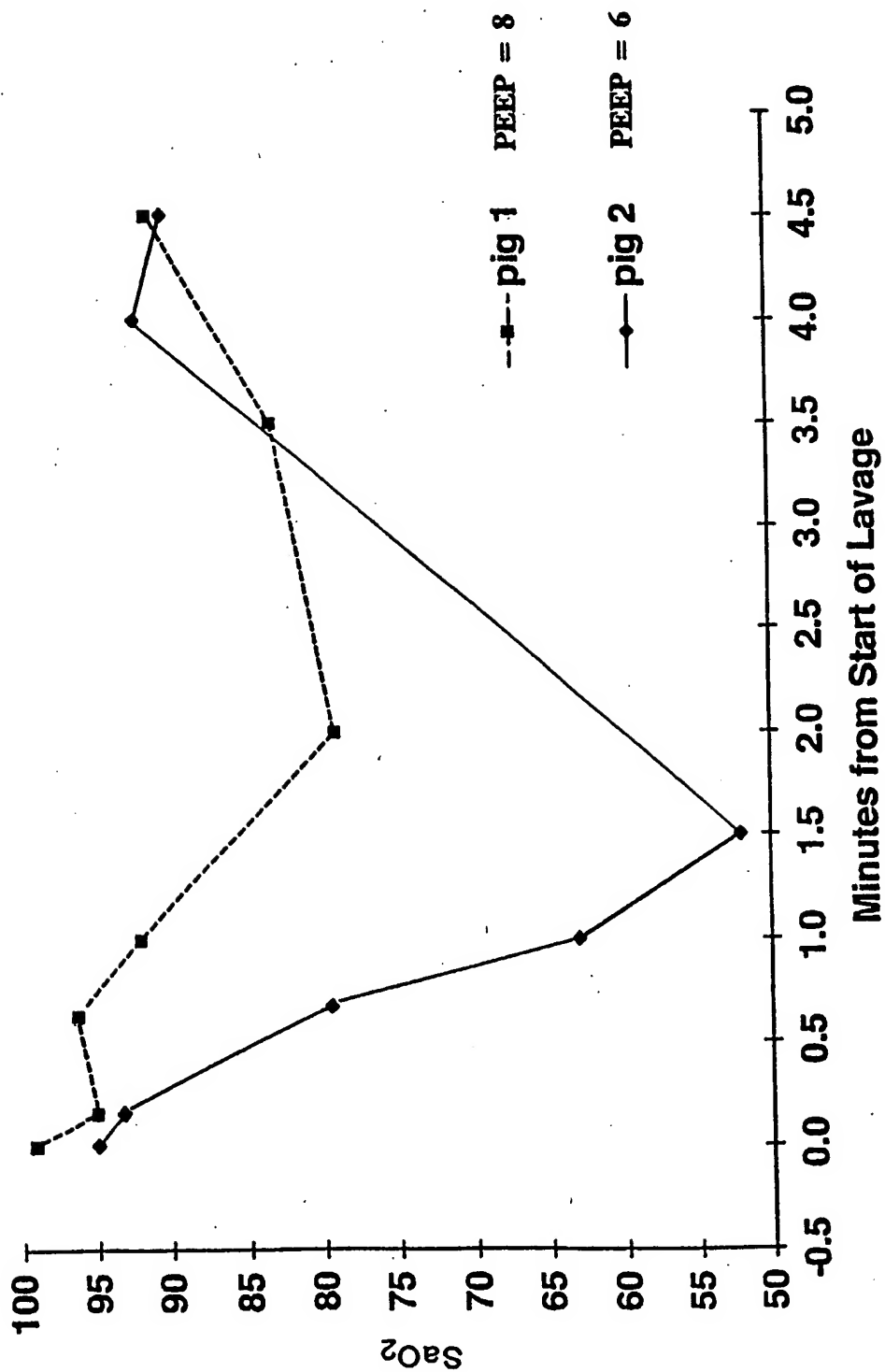


FIG. 13

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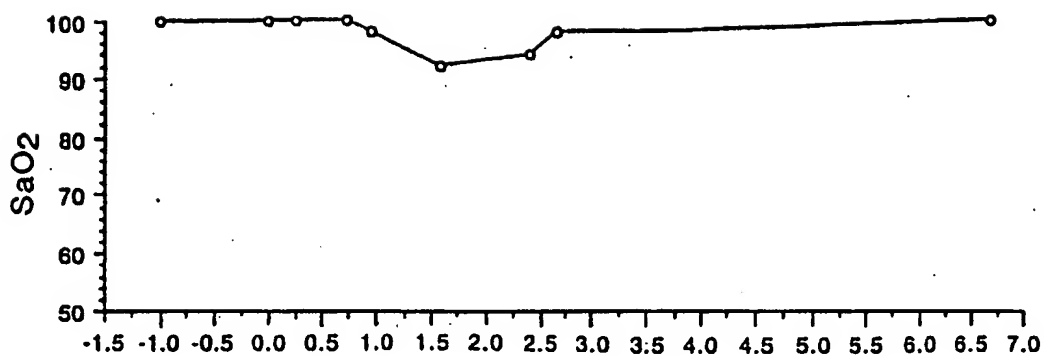


FIG. 14A

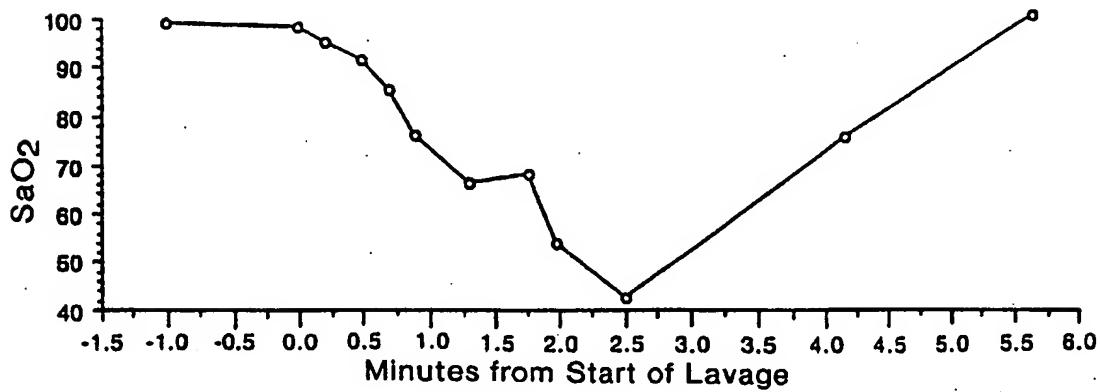


FIG. 14B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/01711

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :C07K 5/10 US CL :514/11,12,13 According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/11,12,13 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS search terms: pulmonary, lavage, positive end-expiratory pressure, PEEP														
C. DOCUMENTS CONSIDERED TO BE RELEVANT														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
X	US 5,407,914 A (COCHRANE et al.) 18 April 1995, col. 1, lines 30-69.	1-57												
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
<table border="0"><tr><td>* Special categories of cited documents:</td><td>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>*A* document defining the general state of the art which is not considered to be of particular relevance</td><td>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>*B* earlier document published on or after the international filing date</td><td>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>*A* document member of the same patent family</td></tr><tr><td>*O* document referring to an oral disclosure, use, exhibition or other means</td><td></td></tr><tr><td>*P* document published prior to the international filing date but later than the priority date claimed</td><td></td></tr></table>			* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family	*O* document referring to an oral disclosure, use, exhibition or other means		*P* document published prior to the international filing date but later than the priority date claimed	
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<p>(21) International Application Number: PCT/US98/13868 (22) International Filing Date: 2 July 1998 (02.07.98) (30) Priority Data: 08/887,206 2 July 1997 (02.07.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/887,206 (CON) Filed on 2 July 1997 (02.07.97) (71) Applicant (for all designated States except US): BRONCUS TECHNOLOGIES, INC. [US/US]; Building A, Suite 8, 1400 N. Shoreline Boulevard, Mountain View, CA 94043 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): LAUFER, Michael, D. [US/US]; 1259 El Camino Real #211, Menlo Park, CA 94025 (US). (74) Agents: KREBS, Robert, E. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: BLEB REDUCER</p> <div data-bbox="308 1176 1282 1449"></div> <p>(57) Abstract</p> <p>A device (10) and method for treating hollow, elastic body structures such as blebs in lungs, are provided. The device (10) includes an elongated member (10) having a heating element that comprises one or more energy delivery members (12, 14, 16, 18). The method includes heating said body structure to cause at least a portion of the crosslinks of the collagen in the wall to unlink/open and subsequently form new crosslinks after the diameter of said body structure has been significantly reduced and collagen fibers have realigned.</p>		

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BLEB REDUCER

Field of the Invention

The present invention relates to a device and method for treatment of hollow, elastic body structures and more particularly for treatment of blebs in the lungs.

5

Background of the Invention

Blebs are abnormal vacuoles in the lungs which may range from about 3 mm to several centimeters in size. Blebs often develop when alveolar walls deteriorate thereby transforming a mass of individual alveoli into one or more blebs. The alveoli are small, polyhedral recesses composed of a fibrillated connective tissue and surrounded by a few involuntary muscular and elastic fibers. As is apparent, the presence of blebs adversely affects the respiratory function of the lungs by inducing the surface area available for actual gaseous exchange in respiration. For severe cases, surgeons have endeavored to alleviate the disabling conditions associated with blebs by removing portions of lungs containing blebs. These operations are quite risky and are considered final options.

Notwithstanding the conventional treatments available, there exists a need in the art for an effective treatment for conditions associated with blebs and other hollow, elastic body structures. Specifically, there is a need for effective treatment which only requires minimal surgery.

20

Summary of the Invention

The present invention is based in part on the discovery that the size of a bleb can be significantly reduced by subjecting the surface of the bleb to a sufficient amount of heat to cause at least a portion of the crosslinks of the collagen fibers to open and subsequently form new cross links after the collagen fibers have realigned.

25

In one aspect, the invention is directed to an apparatus for treating hollow, elastic body structures such as blebs in the lungs which includes a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes
5 the wall of said structure to undergo a structural transformation effective to reduce the size of said structure, a means for attaching the treatment device to a surface of said structure, and a source of energy that is conducted to the heating element.

In another aspect, the invention is directed to an apparatus for treating a
10 bleb which defines a cavity which includes a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen, a source of energy that is
15 conducted to the heating element, and means for removing air from the cavity.

The invention is further directed to methods of treating and removing hollow, elastic body structure such as a bleb. One method includes the procedure of heating the wall of said structure with sufficient energy to cause the wall to undergo a structural transformation which effectively reduces the size of said
20 structure. Another method includes the procedure of removing air from the cavity of said structure to reduce the size of the cavity. This procedure effectively reduces the size of said structure. Furthermore, the method may include heating and sealing the air passage(s) or channel(s) leading to the cavity and thereby fix the size of a bleb. In one application the bronchiole leading to
25 the bleb is heated to seal the bronchiole lumen thereby preventing the bleb from redeveloping.

Brief Description of the Drawings

As used herein, like reference numerals will designate similar elements in the various embodiments of the present invention wherein:

Figures 1, 1A, 1B and 1C illustrate an embodiment of the treatment
5 apparatus;

Figure 2 illustrates implementation of the treatment apparatus through a partially exposed and enlarged section of lung tissue;

Figures 3 and 4 illustrate a bronchoscope; and

Figure 5 illustrates an embodiment of the treatment apparatus.

Detailed Description of the Preferred Embodiments

The present invention is directed to devices and methods for treating hollow, elastic body structures that are typically abnormal manifestations. These structures have cavities whose walls contain collagen. As further described herein the collagen will respond to heat treatment thereby reducing the size of the
15 cavities. Prior to treatment, these cavities may range from about 3 mm to several centimeters in size. The invention is particularly suited for treating blebs in the lungs. The invention will be described using the treatment of blebs as the illustrative example, however, it is understood that the invention is applicable generally to the treatment of hollow, elastic body structures.

20 FIG. 1 illustrates an embodiment of the inventive treatment apparatus which includes an elongated, cylindrical member 10 having a heating element that has a plurality of electrodes designated 12, 14, 16 and 18, each having an exposed distal end which may be substantially flush with the surface of the distal end 20 of the member. The electrodes are electrically connected to a source of
25 RF energy via connector 22. Preferably the exposed surface of the electrodes collectively has a surface area of about 10 mm² to about 100 cm². The treatment apparatus has an outer diameter that is small enough to enter a bleb or can be expanded to fill the bleb or can be expanded to fill the bleb as further described

herein. Typically, the outer diameter ranges from about 2 French to about 8 French prior to any expansion.

The function of the heating element is to apply a sufficient amount of energy to the walls of a bleb to cause collagen to undergo a structural transformation to cause the walls to shrink. In this embodiment, energy
5 emanates from the exposed distal ends from the electrodes so that following treatment with this particular apparatus, the size of the bleb is significantly reduced or the bleb is eliminated altogether. As is apparent, the number and surface area of each electrode are not critical. In the case where the surface area
10 is small relative to the diameter of the bleb, it may be necessary to move the apparatus and heat more than one area of the wall in order to transform sufficient amounts of the collagen to reduce the size of the bleb and to distribute the heat more uniformly.

The heating element is made of any suitable biocompatible material such
15 as, for example, conductive polymer, stainless steel, platinum, other noble metals, or shape memory alloy, such as nickel-titanium-alloy (Nitinol™ commercially available from Raychem Corporation, Menlo Park, CA). Member
10 is made of a flexible material so that it can be maneuvered through a catheter or bronchoscope as described herein. The term "catheter" refers generally to a
20 tubular device suitable for insertion into the a bleb through the bronchioles. A bronchoscope is a modified catheter which is an illuminating instrument for inspecting and passing instruments (e.g., treatment device) into the bronchioles.

When the treatment apparatus is positioned at the treatment site, an RF
generator is activated to provide suitable RF energy, preferably at a selected
25 frequency in the range of 10 MHz to 1000 MHz. The emitted energy is converted within the tissue into heat in the range of about 40°C to about 95°C. As the temperature increases, it is believed that the collagen undergoes a structural transformation whereby the collagen fibers contract and new cross links are formed.

RF energy is no longer applied after there has been sufficient transformation, e.g., shrinkage, of the collagen fibers which may be gauged by removing the heating device from the treatment site and conducting a visual inspection. Sufficient shrinkage may also be detected by fluoroscopy, external
5 ultrasound scanning, pulse-echo ultrasound scanning, sensing the collapsing or straightening of the heating element with appropriate feedback variables, impedance monitoring or any other suitable method for pulmonary function testing.

Substantial transformation may be achieved very rapidly, depending upon
10 the specific treatment conditions. Because the transformation can proceed at a rather rapid rate, the RF energy should be applied at low power levels. Preferably, the RF energy is applied for a length of time in the range of about 1 second to about 120 seconds. Suitable RF power sources are commercially available and well known to those skilled in the art. In one embodiment the RF
15 generator employed has a single channel, delivering approximately 1 to 10 watts of RF energy and possessing continuous flow capability. The rate of transformation can be controlled by varying the energy delivered to the heating element.

Besides using RF energy for energizing the heating element, it is to be
20 understood that other forms of energy such as alternating current, microwaves, ultrasound, and light either coherent (e.g., laser) or incoherent (e.g., light emitting diode or tungsten filament) can be used, and that the thermal energy generated from a resistive coil, a hot fluid element (e.g., circulating liquids, gases, combinations of liquids and gases, etc.), a curie point element, or similar
25 elements can be used as well. The hot fluid element may comprise, for example, an elongated member similar to the one illustrated in FIG. 1 that includes a conduit system whereby heated fluid is transported through the member and then channeled outward toward the surface of the distal end 20 of the member. Regardless of the source, the energy delivered to the bleb wall should not ablate
30 the tissue.

The heating element, as shown in FIG. 1, operates as a unipolar, internal electrode in the patient's body. An outer electrode (not shown) having a much larger surface area than that of the electrode bands is placed on the outer surface of the patient's body. For example, an external metal mesh or solid plate is placed on the skin. Both electrodes are connected to an RF generator which produces an electric field at a high frequency within the patient's body. Because the collective surface area of the electrode bands is much smaller than that of the outer electrode, the density of the high frequency electric field is much higher around the electrode bands. The electric field reaches its highest density between the two electrodes in the region near the heating element. The increased density of the field around the distal ends of the electrodes produces localized heating of the tissue of the bleb wall.

A heating element comprising a bipolar electrode can also be used. Referring to FIG. 1, in such a bipolar electrode arrangement, electrodes 12 and 16 can be connected to the positive electrode of the RF generator and electrodes 14 and 18 are connected to the negative electrode. The material between the conductive elements are electrically insulated. In this case, FIG 1 illustrates a heating element having multiple, i.e., double, bipolar electrodes. The electrodes emit RF energy with the first conductive element acting as the active electrode and the second conductive element acting as the return electrode, or vice versa.

The treatment apparatus preferably includes a device for attaching the apparatus to the bleb wall. FIG. 1A illustrates one device which comprises a plurality of generally axially extending hooks 30 that are made of metal or other suitable material. FIG. 1B illustrates another device which comprises expandable prongs 32. The hook and prong devices are sized to be received with lumen 24 of the treatment apparatus.

The treatment apparatus can be maneuvered to a particular bleb initially through the bronchus, which upon entering the substance of the lung, divides and subdivides bipinnately, throughout the entire organ. Sometimes multiple branches arise together, and occasionally small lateral branches are given off

from the sides of a main trunk. Each of the smaller subdivisions of the bronchi enters a pulmonary lobule, and is termed a lobular bronchial tube or bronchiole. The bronchiole becomes enlarged, and is termed the atrium or alveolar passage; from it are given off, on all sides, ramifications, called infundibula, which are
5 closely beset in all directions by alveoli.

In operation, after the treatment apparatus is maneuvered to the bleb surface through the bronchiole, the hooks or prongs are projected from lumen 24 when the surgeon engages (e.g., presses) actuator 36 which is connected to the hooks or prongs via a stiff wire. The hooks or prongs are then manipulated to
10 fasten onto tissue on the bleb surface whereupon the actuator is disengaged and the hooks or prongs are retracted. In this fashion, the bleb tissue becomes attached to the treatment apparatus and as a corollary the heating element becomes positioned adjacent to (or is in physical contact with) the bleb surface.

The treatment apparatus may further include an inflatable balloon device
15 76 which is made of a flexible, expandable material. As shown in FIG. 1C, the apparatus includes at least two internal passageways 82 and 84. For example, passageway 82 may be in communication with lumen 24 and passageway 84 may be in communication with the balloon device.

In operation, as illustrated in FIG. 2, after the treatment apparatus is
20 inserted into the bronchiole 90 which leads to bleb 92, the balloon device is inflated with air or other suitable fluid so that the outer surface of the balloon is in physical contact with the inner surface of the bronchiole. Next the air is withdrawn from the bleb through lumen 24 and via passageway 84 which in turn is connected to an aspirator device (not shown). The suction will cause the size
25 of the bleb to decrease. Once the size of the bleb has been reduced sufficiently so as to be in contact with the distal ends of the electrodes, the heating elements can be energized to complete the treatment process. The treatment apparatus may include a conventional pressure sensing gauge 21 to measure the pressure in the cavity of the bleb.

The segment of the treatment apparatus forming the balloon is fabricated of material that is expandable and substantially impervious to air or other suitable gases. In this fashion, this section of the elongated member is radially expandable and deformable in response to compressed gas or any other suitable force or material that is applied into the interior region of the elongated member. Moreover, the elongated member will substantially return to its original, non-expanded form when the internal force is deactivated or the material is withdrawn.

FIGS. 3 and 4 illustrate a bronchoscope 30 having treatment apparatus 10 slidably positioned within a lumen. The device also includes an image-transmitting fiber 50 and illuminating fiber 52. Any conventional bronchoscope with an appropriately sized and directed working lumen may be employed. The image transmitting fiber collects light from the distal end of the treating apparatus and directs the light to a viewing apparatus (not shown) for displaying an image of the obstructed air passage. The bronchoscope may have a panning system which enables the tips to be moved in different directions.

When treating a particular site, excessive fluid is first removed from the bleb by conventional means such as with a suction catheter. Thereafter, the bronchoscope can be advanced from the person's nasal or oral cavity, and through the trachea, main stem bronchus, and into a bleb. The heat treatment device is connected to an RF generator which could be located in the handle of the device or located remotely from the patient.

The treatment device is advanced forward from the bronchoscope before the attachment means (e.g., hook or prong device) is actuated. Thereafter, the RF generator is energized. Depending on the number of, and/or surface area of, the electrodes, the treatment device can be moved to another position for further heat treatment. After completion of the treatment, RF energy to the electrodes is discontinued, the attachment means released, and the bronchoscope is then removed from the patient.

The heating apparatus can be made to provide protection against overheating of the connective tissue which may cause the collagen to denature. Temperature monitoring and impedance monitoring can be utilized in a system which provides feedback to the user in the form of sounds, lights, other displays or which shuts down the application of energy from the heating element to the treatment site when sufficient transformation is detected and to avoid burning of the treatment site. The amount of energy applied can be decreased or eliminated manually or automatically under certain conditions. For example, the temperature of the wall of the air passage, or of the heating element can be monitored and the energy being applied adjusted accordingly. The surgeon can, if desired, override the feedback control system. A microprocessor can be included and incorporated into the feedback control system to switch the power on and off, as well as modulate the power. The microprocessor can serve as a controller to monitor the temperature and modulate the power. Similarly, the treatment device can provide feedback protection against excessive suction of the cavity and/or excessive inflation of the balloon.

FIG. 5 illustrates an embodiment of another inventive treatment apparatus which includes an elongated, cylindrical member 50 having a heating element that has a plurality of electrodes designated 62 and 64 located on the outer surface of the member. The electrodes are electrically connected to a source of RF energy via connector 68. Preferably each electrode is configured as a band as shown that has a width of about 0.5 mm to about 3 mm and preferably each electrode band is separated from the next by a distance of about 1 mm to 5 mm. It is understood that the heating element comprises one or more electrode bands. The apparatus has a distal end 70 that is parabolically-shaped to reduce the amount of resistance encountered when the apparatus is advanced into the air passages. The distal end includes lumen 72 which can accommodate attachment devices shown in FIGS 1A and 1B. The apparatus further includes a balloon device 86 which is depicted in the inflated position.

The apparatus has an outer diameter that is approximately equal to (or can be expandable to equal) the desired final inner diameter of a bronchiole that leads to a bleb to be treated. Typically, the outer diameter ranges from about 2 French to about 6 French.

5 The function of the treating element is to apply a sufficient amount of energy to the walls of a bronchiole to cause collagen in the walls to undergo a structural transformation to seal the lumen. As is apparent, the number and width of each electrode band are not critical. In the case where there is only one electrode band, it may be necessary to move the apparatus and heat more than
10 one area of the lumen wall in order to transform sufficient amounts of the collagen. Member 50 is also preferably made of a flexible material so that it can be maneuvered through a catheter or bronchoscope as described herein.

The treatment apparatus can be inserted into a bronchiole which leads to the cavity of the bleb. Thereafter, the balloon device is inflated with air or other
15 suitable fluid so that the outer surface of the balloon is in physical contact with the inner surface of the bronchiole. A conventional pressure gauge 85 may be incorporated which can be employed as a feedback mechanism to avoid overinflation, for example. Next the air is withdrawn from the bleb through lumen 72 which is connected to an aspirator device (not shown). The aspirator
20 will create sufficient suction to cause collapse of the bleb wall and ultimately reduce the size of the bleb cavity.

When the suction is applied, tissue forming the bleb wall is drawn toward lumen 72 and eventually the bleb becomes invaginated or turned inside out as tissue enters inside the lumen. To facilitate the heating of this tissue, in one
25 embodiment, the apparatus shown in FIG. 5, electrode 88 is positioned in the inside surface of lumen 72. In this fashion, as bleb tissue is pulled into the lumen by the suction, the invaginated bleb can be heat sealed by electrode 88. Alternatively, the electrodes can be positioned at the tip of the apparatus for heating the bronchiole that leads to the bleb or to seal the bronchiole to the
30 invaginated bleb. Either way, the balloon remains inflated during the heat

treatment process to maintain the vacuum. To facilitate this procedure, electrode bands can be positioned near the distal portion 70 of the treatment apparatus. Moreover, the distal portion can be tapered so that treatment apparatus can be gradually withdrawn from the bronchiole lumen as its diameter decreases.

5 When the treatment apparatus is positioned at the treatment site, an RF generator is activated to provide suitable RF energy, preferably at a selected frequency in the range of 10 MHz to 1000 MHz. The emitted energy is converted within the tissue into heat in the range of about 40°C to about 95°C. RF energy is no longer applied after there has been sufficient transformation,
10 e.g., shrinkage, of the collagen fibers which may be gauged by removing the heating device from the treatment site and visually determining whether the lumen remains uncollapsed. Sufficient shrinkage may also be detected by fluoroscopy, external ultrasound scanning, pulse-echo ultrasound scanning, sensing the collapsing or straightening of the heating element with appropriate
15 feedback variables, impedance monitoring or any other suitable method.

Besides using RF energy for energizing the heating element, it is to be understood that other forms of energy such as those described for the device of FIG. 1 including alternating current, microwaves, ultrasound, and light either coherent (e.g., laser) or incoherent (e.g., light emitting diode or tungsten
20 filament) can be used, and that the thermal energy generated from a resistive coil, a hot fluid element (e.g., circulating liquids, gases, combinations of liquids and gases, etc.) can be used as well.

The heating element, as shown in FIG. 5 operates as a unipolar, internal electrode in the patient's body. An outer electrode (not shown) having a much
25 larger surface area than that of the electrode bands is placed on the outer surface of the patient's body. A heating element comprising a bipolar electrode can also be used.

While the heating elements have been shown as electrode bands, other configurations can be used such as, for example, spiral, ring and grid patterns.
30 These elements will create corresponding patterns on the lumen wall. One

limitation is that the heating elements have sufficient surface area in contact with the wall of the lumen so that the heat treatment process can be completed within a reasonable time.

5 The invention is also directed to the demonstration or instruction of the inventive surgical techniques including, but not limited to, actual instructions involving patients, audio-visual presentations, animal demonstrations, and the like.

10 While several particular embodiments of the invention have been illustrated and described, it will be apparent that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is Claimed Is:

1. An apparatus for treating an elastic body structure that defines a cavity which comprises:
a treatment device comprising an elongated member and a heating element
5 that comprises one or more energy delivery members which when energized causes the wall of the cavity to undergo a structural transformation effective to reduce the size of the cavity;
means for attaching the treatment device to a surface of the cavity; and
a source of energy that is conducted to the heating element.
- 10 2. The apparatus of claim 1 wherein the source of energy produces energy in a form that is selected from the group consisting of RF energy, alternating current, microwaves, ultrasound, coherent light, incoherent light, thermal energy, and mixtures thereof.
3. The apparatus of claim 2 wherein the one or more energy delivery
15 members each comprise an electrode and wherein a segment of the elongated member comprises elastic material and wherein each electrode has a distal portion that is positioned on an outer surface of the segment.
4. The apparatus of claim 1 wherein the one or more energy delivery
20 members comprise one or more sets of double electrode bands wherein each set comprises a first electrode which is connected to the positive electrode of an RF generator and a second electrode which is connected to the negative electrode of the RF generator.
5. The apparatus of claim 1 wherein the one or more energy delivery members emit light energy.

6. The apparatus of claim 1 wherein the one or more energy delivery members comprise a conduit that channels heated fluid into and out of the elongated member.
7. The apparatus of claim 1 wherein the source of energy comprises a radio frequency generator.
8. The apparatus of claim 1 further comprising a feedback indicator.
9. The apparatus of claim 8 wherein the feedback indicator is an auditory signal.
10. The apparatus of claim 8 wherein the feedback indicator is a visual signal.
11. The apparatus of claim 8 wherein the feedback indicator is indicative of shrinkage.
12. The apparatus of claim 8 wherein the feedback indicator is indicative of temperature.
13. The apparatus of claim 8 wherein the feedback indicator is indicative of electrical characteristics.
14. The apparatus of claim 8 wherein the feedback indicator is indicative of pressure within the cavity.
15. The apparatus of claim 1 wherein the means for attaching the treatment device comprises hooks or prongs.

16. The apparatus of claim 1 wherein the treatment device has a tubular member on an outer surface of the elongated member and wherein the elongated member defines a first diameter and the tubular member having a second, expanded and deformed diameter upon an application of a radially,
5 outwardly extending force.

17. The apparatus of claim 1 wherein the heating elements further comprise one or more electrode bands that are each spaced apart from an adjacent band.

18. The apparatus of claim 1 wherein the treatment device comprises
10 means for removing air from the cavity.

19. The apparatus of claim 18 wherein the means for removing air comprises a lumen in the treatment device that is in communication with an aspirator.

20. The apparatus of claim 19 wherein the heating element is located
15 on an inner surface of the lumen.

21. An apparatus for treating a bleb which defines a cavity which comprises:

a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized
20 causes the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and to seal the bronchiole lumen;

a source of energy that is conducted to the heating element; and
means for removing air from the cavity.

22. The apparatus of claim 21 wherein the one or more energy delivery members each comprises an electrode band.

23. The apparatus of claim 22 wherein each electrode is positioned on an outer surface of the segment.

5 24. The apparatus of claim 21 wherein the one or more energy delivery members comprise one or more sets of double electrode bands wherein each set comprises a first electrode which is connected to the positive electrode of an RF generator and a second electrode which is connected to the negative electrode of the RF generator.

10 25. The apparatus of claim 21 wherein the one or more energy delivery members emit light energy.

26. The apparatus of claim 21 wherein the one or more energy delivery members comprise a conduit that channels heated fluid into and out of the elongated member.

15 27. The apparatus of claim 21 wherein the source of energy comprises a radio frequency generator.

28. The apparatus of claim 21 further comprising a feedback indicator.

20 29. The apparatus of claim 28 wherein the feedback indicator is an auditory signal.

30. The apparatus of claim 28 wherein the feedback indicator is a visual signal.

25

31. The apparatus of claim 28 wherein the feedback indicator is indicative of shrinkage.

32. The apparatus of claim 28 wherein the feedback indicator is
5 indicative of temperature.

33. The apparatus of claim 28 wherein the feedback indicator is indicative of electrical characteristics.

34. The apparatus of claim 21 wherein the means for attaching the
10 treatment device comprises hooks or prongs.

35. The apparatus of claim 21 wherein the treatment device has a tubular member on an outer surface of the elongated member wherein the elongated member defines a first diameter and the tubular member having a second, expanded and deformed diameter upon an application of a radially,
15 outwardly extending force, which second diameter is variable and dependent upon the amount of force applied to the tubular member.

36. The apparatus of claim 35 wherein the means for removing air comprises a lumen in the treatment device that is in communication with aspirator.

37. The apparatus of claim 36 wherein the heating element is located
20 on an inner surface of the lumen.

38. A method of treating an elastic body structure that defines a cavity in an individual that comprises the step of:

heating a surface of said structure to a temperature effective to cause the wall of the cavity to undergo a structural transformation to reduce the size of the cavity.

39. The method of claim 38 wherein the wall of the cavity is heated to
5 a temperature in the range between about 40°C and about 95°C.

40. The method of claim 39 wherein the wall is heated for about 1 to about 120 seconds.

41. The method of claim 38 wherein the step of heating the surface comprises:
10 advancing a treatment apparatus into said structure of the individual; and energizing the treatment apparatus to raise the temperature of the surface to cause the wall of the cavity to undergo a structural transformation.

42. The method of claim 41 wherein the treatment apparatus comprises:
15 a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes the wall of said structure to undergo a structural transformation effective to reduce the size of the cavity;
means for attaching the treatment device to a surface of said structure; and
20 a source of energy that is conducted to the heating element.

43. A method of treating a bleb which defines a cavity in the lung of an individual that comprises the steps of:
removing air from the cavity through a bronchiole that is in communication with the cavity to cause a reduction in size of the cavity; and
25 heating the wall of the bronchiole to seal the bronchiole lumen.

44. The method of claim 43 wherein the wall of the bronchiole is heated to a temperature in the range between about 40°C and about 95°C.

45. The method of claim 44 wherein the wall of the bronchiole is heated for about 1 to about 120 seconds.

5 46. The method of claim 43 wherein the step of heating the wall of the bronchiole comprises:

 advancing a treatment apparatus into a lumen of the bronchiole;

 energizing the treatment apparatus to raise the temperature of the surface of the wall to cause the wall to undergo a structural transformation.

10 47. The method of claim 46 wherein the treatment apparatus comprises:

 a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes the wall of a bronchiole that is in communication with the bleb to undergo

15 a structural transformation effective to reduce the size and seal the bronchiole;

 a source of energy that is conducted to the heating element; and

 means for removing air from the cavity.

20 48. A method of treating a bleb which defines a cavity in the lung of an individual that comprises the steps of:

 drawing air from the cavity to cause a reduction in size of the cavity; and
 heating a surface of the bleb wall to seal the cavity.

49. The method of claim 48 wherein the step of drawing air from the cavity causes the wall of the bleb to invaginate.

50. The method of claim 49 wherein heating the surface of the bleb wall fixes the size of the bleb.

51. The method of claim 48 wherein the wall of the bleb is heated to a
5 temperature in the range between about 40°C and about 95°C.

52. The method of claim 51 wherein the wall of the bleb is heated for about 1 to about 120 seconds.

53. The method of claim 48 wherein the step of drawing air from the cavity comprises:

- 10 (a) advancing a treatment apparatus into a lumen of the bronchiole that is in communication with the cavity wherein the treatment apparatus comprises:
- (i) an elongated member and a heating element that
comprises one or more energy delivery members which when energized causes
15 the bleb wall to undergo a structural transformation effective to reduce the size and seal the bleb;
- (ii) a source of energy that is conducted to the heating
element; and;
- (iii) means for removing air from the cavity; and
- 20 (b) activating said means for removing air.

54. The method of claim 53 wherein the means for removing air comprises a lumen in the treatment apparatus that is in communication with an aspirator.

25 55. The method of claim 54 wherein the heating element is located on an inner surface of the lumen.

56. A method of training a person to treat an elastic body structure that defines a cavity in an individual that comprises demonstrating or instructing the performance of the following steps:

5 heating a surface of said structure to a temperature effective to cause the wall of the cavity to undergo a structural transformation to reduce the size of the cavity.

57. The method of claim 56 wherein the wall is heated to a temperature in the range between about 40°C and about 95°C.

10 58. The method of claim 57 wherein the wall is heated for about 1 to about 120 seconds.

59. The method of claim 56 wherein the step of heating the surface comprises:

15 advancing a treatment apparatus into the bleb of the individual;
energizing the treatment apparatus to raise the temperature of the surface to cause the wall of the cavity to undergo a structural transformation.

60. The method of claim 59 wherein the treatment apparatus comprises:

20 a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized causes the wall of the said structure to undergo a structural transformation effective to reduce the size of the cavity;
means for attaching the treatment device to a surface of said structure; and
a source of energy that is conducted to the heating element.

61. A method of training a person to treat a bleb which defines a cavity in the lungs of an individual that comprises demonstrating or instructing the performance of the following steps:

5 removing air from the cavity through a bronchiole that is in communication with the cavity to cause a reduction in size of the cavity; and heating the wall of the bronchiole to seal the bronchiole lumen.

62. The method of claim 61 wherein the wall of the bronchiole is heated to a temperature in the range between about 40°C and about 95°C.

63. The method of claim 62 wherein the wall of the bronchiole is
10 heated for about 1 to about 120 seconds.

64. The method of claim 61 wherein the step of heating the wall of the bronchiole comprises:
advancing a treatment apparatus into a lumen of the bronchiole;
energizing the treatment apparatus to raise the temperature of the surface
15 of the wall to cause the wall to undergo a structural transformation.

65. The method of claim 64 wherein the treatment apparatus comprises:
a treatment device comprising an elongated member and a heating element that comprises one or more energy delivery members which when energized
20 causes the wall of a bronchiole that is in communication with the bleb to undergo a structural transformation effective to reduce the size and seal the bronchiole;
a source of energy that is conducted to the heating element; and
means for removing air from the cavity.

66. A method of training a person to treat a bleb of an individual which defines a cavity in the lung of the individual that comprises demonstrating or instructing the following steps of:

5 drawing air from the cavity to cause a reduction in size of the cavity; and heating a surface of the bleb wall to seal the cavity.

67. The method of claim 66 wherein the step of drawing air from the cavity causes the wall of the bleb to invaginate.

68. The method of claim 67 wherein the step of heating the surface of the bleb wall comprises heating a surface of the invaginated bleb which fixes the size of the bleb.

69. The method of claim 66 wherein the wall of the bleb is heated to a temperature in the range between about 40°C and about 95°C.

70. The method of claim 69 wherein the wall of the bleb is heated for about 1 to about 120 seconds.

71. The method of claim 66 wherein the step of drawing air from the cavity comprises:

(a) advancing a treatment apparatus into a lumen of the bronchiole that is in communication with the cavity wherein the treatment apparatus comprises:

20 (i) an elongated member and a heating element that comprises one or more energy delivery members which when energized causes the bleb wall to undergo a structural transformation effective to reduce the size and seal the bleb;

25 (ii) a source of energy that is conducted to the heating element; and;

- (iii) means for removing air from the cavity; and
(b) activating said means for removing air.

72. The method of claim 71 wherein the means for removing air comprises a lumen in the treatment apparatus that is in communication with an aspirator.
5

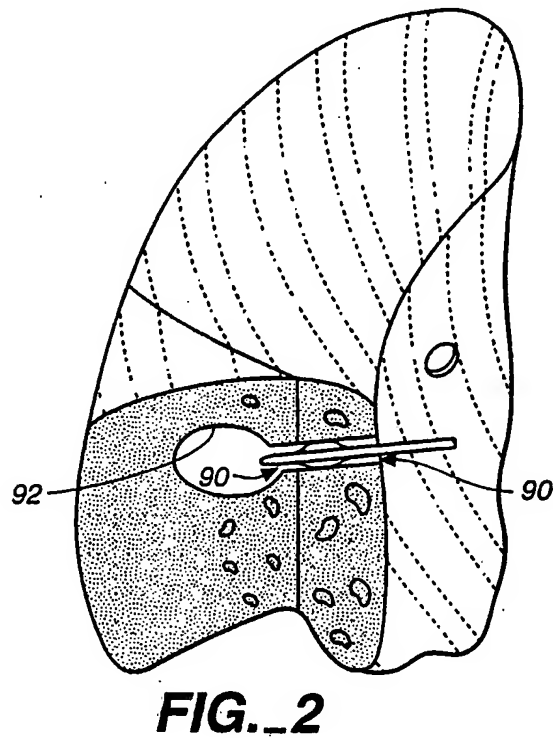
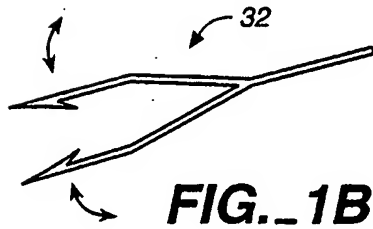
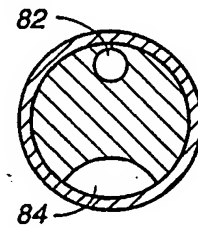
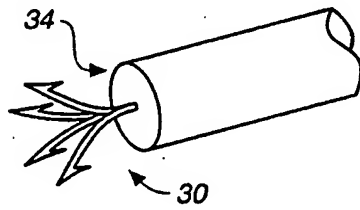
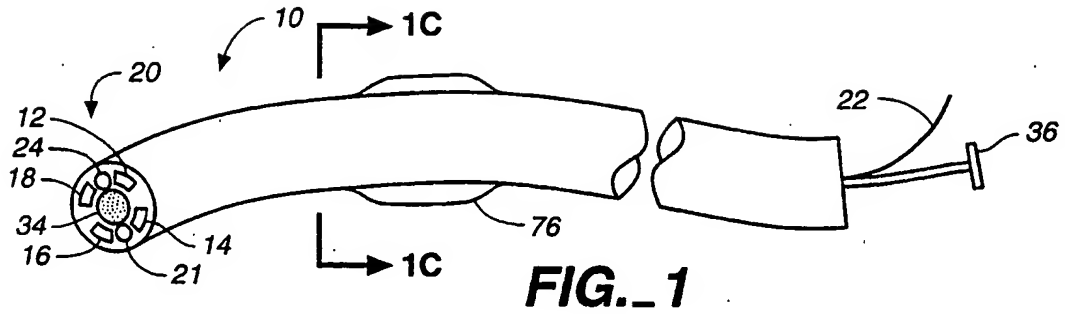
73. The method of claim 72 wherein the heating element is located on an inner surface of the lumen.

74. A modified lung wherein a bleb has been treated by a process that comprises the step of:
10 heating a surface of the bleb to a temperature effective to cause the wall of the bleb to undergo a structural transformation to reduce the size of the cavity.

75. A modified lung wherein a bleb defining a cavity in the lung has been treated by a process that comprises the step of:
15 removing air from the cavity through a bronchiole that is in communication with the cavity to cause a reduction in size of the cavity; and heating the wall of the bronchiole to seal the bronchiole lumen.

76. A modified lung wherein a bleb which defines a cavity in the lung has been treated by a process that comprises the steps of:
20 drawing air from the cavity to cause a reduction in size of the cavity; and heating a surface of the bleb wall to seal the cavity.

1 / 2



2 / 2

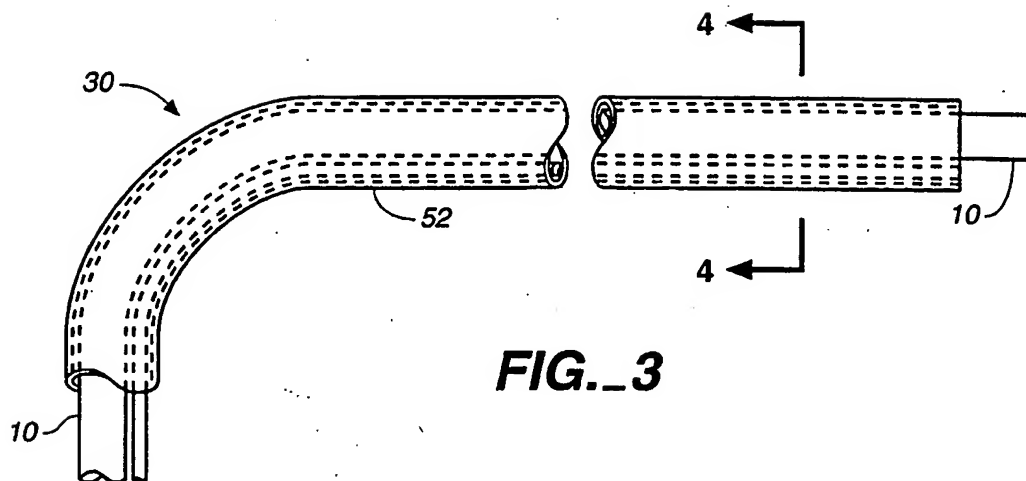


FIG. 3

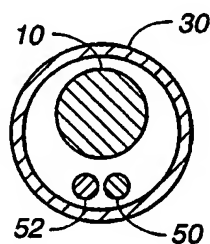


FIG. 4

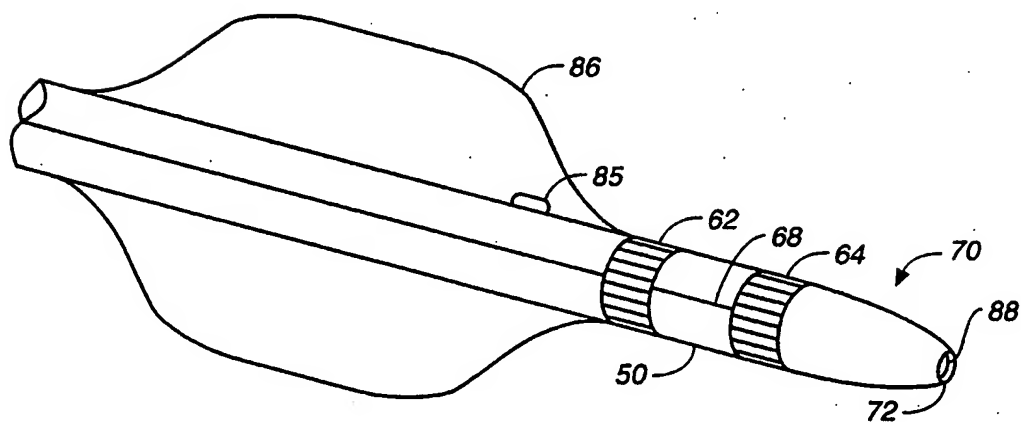


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13868

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 17/38

US CL : 606/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/397; 606/13, 14, 28, 40-42, 46, 48, 49; 607/96, 98-100, 102, 122, 126, 128; 128/397

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STIC

Search Terms: bleb, reduce, heat, electrode, lung, catheter, electrosurgical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 5,507,743 A (EDWARDS et al) 16 April 1996 (16/04/96), Figs. 1-8.	1, 2, 6-8, 10, 12-15 3, 9, 11, 16, 30-33
X	US 5,536,267 A (EDWARDS et al.) 16 July 1996 (16/07/96), Figs. 1-21.	1, 2, 6-8, 10, 12-15
X	US 5,071,222 A (LAAKMANN et al.) 10 December 1991 (10/12/91), Fig. 2.	5
X — Y	US 3,906,955 A (ROBERTS) 23 September 1975 (23/09/75), Fig. 1.	21-23 28-33



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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07 AUGUST 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13868

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,084,045 A (HELENOWSKI) 28 January 1992 (28/01/92), Fig.1.	21-23 ----- 24, 27
X,P	US 5,709,675 A (WILLIAMS) 20 January 1998 (20/01/98), Fig. 2.	21-23
X	US 5,254,117 A (RIGBY et al) 19 October 1993 (19/10/93), Figs. 1 and 9.	1, 18, 19, 34
X --- Y	US 4,672,969 A (DEW) 16 June 1987 (16/06/87), Fig. 3, col. 6 lines 48-54.	38, 39, 41, 42 ----- 40
Y	US 5,586,982 A (ABELA) 24 December 1996 (24/12/96).	3, 16
Y	US 3,929,137 A (GONSER) 30 December 1975 (30/12/75), entire document.	9, 28, 29

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61M 25/00	A2	(11) International Publication Number: WO 99/17827 (43) International Publication Date: 15 April 1999 (15.04.99)
(21) International Application Number: PCT/US98/20800 (22) International Filing Date: 2 October 1998 (02.10.98) (30) Priority Data: 08/943,628 3 October 1997 (03.10.97) US (71) Applicant: SCIMED LIFE SYSTEMS, INC. [US/US]; One SciMed Place, Maple Grove, MN 55311-1566 (US). (72) Inventors: LANGE, Michael, R.; 1415 Wynne Avenue, St. Paul, MN 55108 (US). PEPIN, Henry, J.; 4115 Townline Road, Loretto, MN 55357 (US). (74) Agents: CROMPTON, David, M. et al.; Crompton, Seager & Tufte, LLC, Suite 895, 331 Second Avenue South, Minneapolis, MN 55401-2246 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: BRAIDED ANGIOGRAPHY CATHETER HAVING FULL LENGTH RADIOCAPACITY AND CONTROLLED FLEXIBILITY (57) Abstract A guiding catheter or angiographic catheter for use in cardiovascular interventions which incorporates a low-flexibility multi-layer proximal zone wherein a transition zone separates the proximal zone and a high flexibility distal zone. A mid-region zone transitions the high stiffness of the proximal zone to the higher flexibility of the distal zone to eliminate buckling and kinking. All zones of the catheter have a sufficiently large and substantially similar radiopacity, which allows the entirety of the catheter to be visible in a fluoroscope or other form of X-ray so that the positioning of the catheter can be precisely determined.		

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**BRAIDED ANGIOGRAPHY CATHETER HAVING FULL LENGTH
RADIOPACITY AND CONTROLLED FLEXIBILITY**

Technical Field

This invention relates to the field of intravascular medical devices, and more particularly, to the field of catheters such as angiographic and guide catheters used for the placement of medicines and medical devices within the body. Specifically, the invention is directed to an improved guide or diagnostic catheter having full length radiopacity incorporating a proximal zone having lower flexibility than a distal zone, where a transition zone provides varying flexibility between the proximal zone and the distal zone for improved catheter performance.

Background of the Invention

Angiographic and guide catheters are well known in the field of medicine for use in conjunction with other catheters for the treatment of cardiovascular disease through such procedures as percutaneous transluminal coronary angioplasty (PTCA) procedures. Guide catheters aid in treatment of arterial lesions by providing a conduit for positioning dilatation balloon systems across an arterial stenosis. The need for a greater variety of guide catheters to treat different types of circumstances has grown tremendously as the techniques for the use of such devices has grown.

During the treatment of cardiovascular disease, the catheter must be able to traverse tortuous pathways through blood vessels in a manner that minimizes trauma. In order for the physician to place the catheter at the correct location in the vessel, the physician must apply longitudinal and rotational forces. The catheter must be stiff enough to resist the formation of kinks, while at the same time, the catheter must possess flexibility to be responsive to maneuvering forces when guiding the catheter through the vascular system. The catheter must be rigid enough to push through the blood vessel, but yet flexible enough to navigate the bends in the blood vessel. The guide or angiographic catheter must exhibit good torque control such that manipulation of a proximal portion of the catheter is responsively translated to the tip or distal end of the catheter to curve and guide the catheter through the tortuous pathways. Thus, the catheter must have torsional rigidity to transmit the applied torque. To accomplish this balance between

longitudinal rigidity, torsional rigidity and flexibility, often times a support member is added to the shaft. This support member is often comprised of a metal braid or a coil embedded in the shaft.

In many applications, the catheter is guided through the aorta over the aortic arch
5 and down to the ostium of the vessel which is to be treated. It is preferable to have a soft tip or flexible section engage the ostium. Therefore, it is advantageous to have the proximal section more rigid to transmit the forces applied, but have the distal end more flexible to allow for better placement of the catheter. Having the distal section more flexible also creates a less traumatic section to contact the blood vessel. The distal end
10 of the catheter is rotated, through the transmission of torque from the proximal end, until the tip of the catheter is in the desired position. With the variation of different bend shapes available on the distal ends of these devices and with variations in patient anatomy, each device may need to be torqued more or less in order to correctly place it.

In order to meet these performance requirements, catheters are often
15 manufactured using polymers in conjunction with the above-mentioned support member using a metal braid or coil, wherein the support member is incorporated into the tube of the guide catheter. Catheters can be formed of three layers. An inner tubular member is used which defines an inner lumen which may be formed of a material that decreases the coefficient of friction such as that encountered between a balloon catheter and the
20 inner lumen of the catheter. The support member conforms to the outside of the inner layer and is often comprised of a metal braid or coil. The third outer tube is commonly formed from a polymer and overlays the support member.

In order to meet the above requirements of rigidity and flexibility, a catheter is desired which has regions of varying stiffness which may be readily changed during
25 manufacturing to meet the need for the greater variety of devices necessary to treat different types of circumstances.

An example of one approach is described in U.S. Patent No. 5,533,985, issued July 9, 1996 to James C. Wang, for Tubing, which is incorporated herein by reference. Wang discloses differential stiffness tubing for medical products, including catheters,
30 wherein the tubing has a stiff section and a flexible section joined by a relatively short

transition section in which the materials of the stiff and flexible sections are joined into each other in a smooth gradual manner to produce an inseparable bond between the materials without abrupt joints. This tubing is manufactured using an extrusion process and may be limited in its ability to manufacture catheters having the desired number of regions of varying stiffness and the ability to easily accommodate product design changes during manufacture.

Catheters may be manufactured using this approach, but its practical application may be limited to joining two materials to form two zones of flexibility with a transition therebetween. Thus, with this approach, additional manufacturing steps are necessary to provide for additional regions. These regions of varying stiffness are necessary to provide rigidity to push the catheter through the blood vessel, flexibility to navigate the bends in the blood vessel, and torsional stiffness to correctly place the catheter by maintaining torque control without excessive energy storage which can cause undesirable movement of the catheter end.

It is advantageous that the catheter be visible in a fluoroscope or other form of x-ray, so that the catheter can be positioned with precision. In the prior art, this has been accomplished by applying a metal ring to the catheter adjacent the distal end. It is generally undesirable to place the metal ring exactly on the distal tip of the catheter, since the distal tip needs to be very soft and pliable. Therefore, the metal ring does not completely resolve the problem of precisely locating the distal tip of the catheter within the body by means of a fluoroscope during a medical procedure, since the metal ring is and must be spaced from the distal tip. In other prior art, the distal tip has been manufactured to be substantially more radiopaque than portions of the catheter proximal to the tip.

Summary of the Invention

The present invention overcomes many of the disadvantages found in the prior art by providing a guiding catheter for use in coronary angioplasty and other cardiovascular interventions which incorporates a lower flexibility proximal shaft portion, coupled to a higher flexibility distal tip portion. Within the distal tip, there are three distinct zones of flexibility. A tip transition portion separates a proximal tip portion

from a distal tip portion. The transition portion gradually transitions the lower flexibility of the proximal portion to a higher flexibility of the distal portion via a gradual transition in materials from a higher durometer polymer to a lower durometer polymer to eliminate buckling and kinking. Therefore, when including the flexibility of the proximal shaft portion, the catheter of the present invention includes four distinct zones of flexibility.

The catheter also possesses a high level of radiopacity, said level being substantially similar throughout all portions of the device. It is particularly desirable for all portions of the device to be visible in a fluoroscope or other form of x-ray so that the positioning of the catheter can be precisely determined.

In a preferred embodiment of the present invention, a guide or angiographic catheter is provided comprising a linear shaft and a lumen extending longitudinally through the center of the linear shaft. The linear shaft is comprised of a proximal shaft portion of high radiopacity at the proximal end of the linear shaft, and a distal tip of high radiopacity which extends distally from the distal end of the proximal shaft portion to the distal end of the linear shaft. The distal tip is attached to the distal end of the proximal shaft portion by heat bonding. The radiopacity of all portions of the linear shaft is substantially similar.

The proximal shaft portion further comprises an inner tubular member defining the diameter of the center lumen, an intermediate tubular member overlying and conforming to the inner tubular member, a woven braid member overlying and conforming to the intermediate tubular member, an outer tubular member substantially overlying and conforming to the woven braid member and an outer sleeve tubular member substantially overlying and conforming to the outer tubular member.

The distal tip further comprises a proximal portion having a first material of a first stiffness, a transition portion having a second material with a continuous differential second stiffness, and a distal portion having a third material of a third stiffness. The first stiffness of the first material will be larger than the third stiffness of the third material.

The second stiffness of the second material is defined by a gradual transition from the stiffness of the first material of the proximal portion of the distal tip to the stiffness of the third material of the distal portion of the distal tip.

Brief Description of the Drawings

Other objects of the present invention and many of the attendant advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, in which like reference numerals designate like parts throughout
5 the figures thereof and wherein:

Fig. 1 is a plan view with the manifold cross sectioned of a catheter showing a preferred embodiment of the present invention;

Fig. 2 is a cross section view of Fig. 1 taken along line 2-2;

10 Fig. 3 is a plan view of the distal tip area of the catheter of Fig. 1, illustrating the shaft/tip heat bonding site and the portions of the distal tip including a transition zone of varying stiffness.

Detailed Description of the Preferred Embodiments

Referring now to the drawings, wherein like reference numerals refer to like
15 elements throughout the several views, Fig. 1 is a plan view of a catheter with the manifold shown in cross section showing a preferred embodiment of the present invention. Figure 1 shows a catheter 10 which comprises a hub 46, and a linear shaft 11 having a proximal end 12 and a distal end 14. A central lumen 16 extends longitudinally through the linear shaft from the proximal end 12 to the distal end 14. The linear shaft
20 11 comprises a proximal shaft 17 and a distal tip 20. The proximal shaft 17 has a proximal end 18 and a distal end 19. The distal tip 20 is attached to the distal end 19 of the proximal shaft 17 at the shaft/tip heat bonding site 48.

Referring now to Fig. 2, the proximal shaft portion 17 includes an inner tubular member 22 formed from polyurethane which extends from the proximal end 18 to the
25 distal end 19 of the proximal shaft 17. The inner tubular member 22 defines the inner diameter 21 of the central lumen 16. An intermediate tubular member of polyether block amide copolymer (PEBA) 24, commercially available under the trademark PEBAX, is extruded over the entire length of the inner tubular member 22. The intermediate tubular member of PEBAX 24, has a durometer of 67D, is 80% loaded with a Tungsten filler and
30 a 1% UV stabilizer.

A woven braid member 26 is provided over the entire length of the intermediate tubular member 24. In one embodiment, the intermediate tubular member 24 and woven braid member 26 are passed through a heated dye so that the woven braid member 26 is slightly embedded in the outer surface of the intermediate tubular member 24. In a second embodiment, the intermediate tubular member 24 is substantially cooled before the woven braid member 24 is provided so that the woven braid member 26 is not embedded in the outer surface of the intermediate tubular member 24. The woven braid member 26 is preferably braided from strands of round 0.0020" annealed 304 stainless steel, and has a constant braid density of 40 pic/in over the length of the proximal shaft portion 17.

An outer tubular member 28 is extruded over the entire length of the woven braid member 26. The outer tubular member 28 is preferably manufactured from PEBAX and has a durometer of 67 D, is 80% loaded with a Tungsten filler and a 1% UV stabilizer, and is not translucent. An outer sleeve tubular member of PEBAX 30 is extruded over the entire length of the outer tubular member of PEBAX 28. The outer sleeve tubular member of PEBAX has a durometer of 70 D, and is 30% loaded with a bismuth subcarbonate filler and a colorant (phthalocyanine blue and violet 23).

Referring now to Fig. 3, the distal tip 20 is attached to the distal end 19 of the proximal shaft portion 17 by a heat bonding process. The distal tip 20 has a lumen 34 extending therethrough which defines the central lumen 16 in the distal portion 15. The inner diameter of the tip lumen 36 defined by the distal tip 20 is substantially equal to the inner diameter of the lumen 21 defined by the inner layer of polyurethane 22 of the proximal shaft portion 17. The very distal end of the tip 53 is tapered and the inner diameter within the very distal end of the tip 53 is smaller to fit tightly over a guide wire.

The distal tip 20 is formed from PEBAX using an Interrupted Layer Coextrusion (ILC) process, which in preferred embodiments results in a proximal portion 38, a transition portion 40, a distal portion 42, and a distal end of distal tip 51. The proximal portion 38, transition portion 40, and distal portion 42 preferably have linear dimensions of about 1.25", 1.5" and 1.25", respectively, resulting in a total linear dimension of about 4".

The proximal portion 38 of the distal tip 20 has a durometer of 70 D, and is 55% loaded with a Tungsten filler and a 1% UV stabilizer. The distal portion 42 has a durometer of 47 D, and is also 55% loaded with a Tungsten filler and a 1% UV stabilizer.

5 The transition portion 40 has a durometer ranging from 70 D at the proximal end 43 to 47 D at the distal end 44, as provided by the ILC process. Experiments show that the proximal shaft portion 17 has substantially the same radiopacity as the distal tip 20.

Referring back to Fig. 1, the proximal end 18 of the proximal shaft portion 17 extends into a hub 46 molded directly over the proximal shaft portion 17. A 63 D white PEBAX strain relief is insert molded to the hub, and the proximal shaft portion 17
10 extends into the hub 46 through the PEBAX strain relief 50.

Having thus described the preferred embodiments of the present invention, those of skill in the art will readily appreciate that yet other embodiments may be made and used within the scope of the claims hereto attached.

What is claimed is:

1. A tubular assembly for an intravascular catheter comprising:
a linear shaft having a proximal end, a distal end, and a lumen extending longitudinally therethrough;
5 a proximal shaft portion of high radiopacity included within said linear shaft, said proximal shaft portion extending distally a predefined distance from the proximal end of said linear shaft, wherein said proximal shaft portion has a proximal and distal end;
an inner tubular member contained within said proximal shaft portion;
an intermediate tubular member contained within said proximal shaft portion
10 overlying said inner tubular member and conforming thereto;
a woven braid member contained within said proximal shaft portion overlying said intermediate tubular member and conforming thereto;
an outer tubular member contained within said proximal shaft portion substantially overlying said woven braid member said outer tubular member having a
15 radiopaque agent dispersed therein; and
an outer sleeve overlying at least a portion of said outer tubular member.
2. The tubular assembly of claim 1 wherein the inner tubular member is formed from polyurethane.
20
3. The tubular assembly of claim 1 wherein the intermediate tubular member is formed of polyether block amide, having a durometer of 67 D, loaded with a Tungsten filler and/or UV stabilizer.
- 25 4. The tubular assembly of claim 1 wherein the woven braid member is braided from strands of stainless steel.
5. The tubular assembly of claim 1 wherein said woven braid is embedded in outer surface of said intermediate tubular member.

30

6. The tubular assembly of claim 1 wherein said intermediate tubular member is substantially cooled before said woven braid member is provided so that said woven braid is not embedded in outer surface of said intermediate tubular member.

5 7. The tubular assembly of claim 1 wherein said outer tubular member is formed of polyether block amide having a durometer of 67 D, is 80% loaded with a Tungsten filler and a 1% UV stabilizer.

8. The tubular assembly of claim 1 wherein said outer sleeve tubular member
10 substantially overlies all of said outer tubular member and conforming thereto.

9. The tubular assembly of claim 1 wherein said outer sleeve tubular member is formed from polyether block amide having a durometer of 70D, and is 30% loaded with a bismuth subcarbonate filler and 1% colorant (phthalocyanine blue, violet
15 23).

10. A tubular assembly for an intravascular catheter comprising:
a linear shaft having a proximal end, a distal end, and a lumen extending longitudinally therethrough;
20 a proximal shaft portion of high radiopacity included within said linear shaft, said proximal shaft portion extending distally a predefined distance from the proximal end of said linear shaft, wherein said proximal shaft portion has a proximal end and a distal end; and
a distal tip, said distal tip having a lumen therethrough, said distal tip included
25 within said linear shaft portion extending distally from the distal end of said proximal shaft portion to the distal end of said linear shaft so that said lumen of said proximal shaft portion and said lumen of said distal tip form a continuous lumen extending from said proximal end of said proximal shaft portion through a distal end of said distal tip, said distal tip further comprising a proximal portion having a first material of a first stiffness,
30 a transition portion having a second material with a continuous differential second

stiffness, and a distal portion having a third material of a third stiffness, wherein said transition portion is defined by a gradual transition from said first material of said distal tip proximal portion to said third material of said distal tip distal portion.

- 5 11. The tubular assembly of claim 10 further comprising:
 an inner tubular member contained within said proximal shaft portion;
 an intermediate tubular member contained within said proximal shaft portion
 overlying said inner tubular member and conforming thereto; and
 a woven braid member contained within said proximal shaft portion overlying
10 said intermediate tubular member and conforming thereto.

12. The tubular member of claim 10 wherein the distal tip is heat bonded to
said distal end of said proximal shaft portion.

- 15 13. The tubular member of claim 10 wherein said distal tip is formed from
polyether block amide.

14. The tubular member of claim 10 wherein said proximal portion, said
transition portion, and said distal portion of said distal tip have linear dimensions of about
20 1.25", 1.5" and 1.25", respectively.

15. The tubular member of claim 10 wherein the first stiffness is greater than
the third stiffness.

- 25 16. The tubular member of claim 10 wherein the second continuous differential
stiffness of the second material of the distal tip transition portion is controlled by
controlling the length of the gradual transition from the first material of the distal tip
proximal portion to the third material of the distal tip distal portion.

17. The tubular member of claim 10 wherein substantially all portions of said proximal shaft and said distal tip have substantially similar radiopacity.

18. The tubular assembly of claim 11 wherein the inner tubular member is
5 formed from polyurethane.

19. The tubular assembly of claim 11 wherein the intermediate tubular member is formed of polyether block amide, having a durometer of 67 D, loaded with a Tungsten filler and/or UV stabilizer.
10

20. The tubular assembly of claim 11 wherein the woven braid member is braided from strands of stainless steel.

21. The tubular assembly of claim 11 wherein said woven braid is embedded
15 in outer surface of said intermediate tubular member.

22. The tubular assembly of claim 11 wherein said intermediate tubular member is substantially cooled before said woven braid member is provided so that said woven braid is not embedded in outer surface of said intermediate tubular member.
20

23. The tubular assembly of claim 11 further comprising:
an outer tubular member contained within said proximal shaft portion substantially overlying said woven braid member and conforming thereto.

24. The tubular assembly of claim 23 wherein said outer tubular member is
25 formed of polyether block amide having a durometer of 67 D, is 80% loaded with a Tungsten filler and a 1% UV stabilizer.

25. The tubular assembly of claim 24 further comprising:

an outer sleeve tubular member contained within said proximal shaft portion substantially overlying said outer tubular member and conforming thereto.

26. The tubular assembly of claim 25 wherein said outer sleeve tubular member
5 is formed from polyether block amide having a durometer of 70D, and is 30% loaded with a bismuth subcarbonate filler and 1% colorant (phthalocyanine blue, violet 23).

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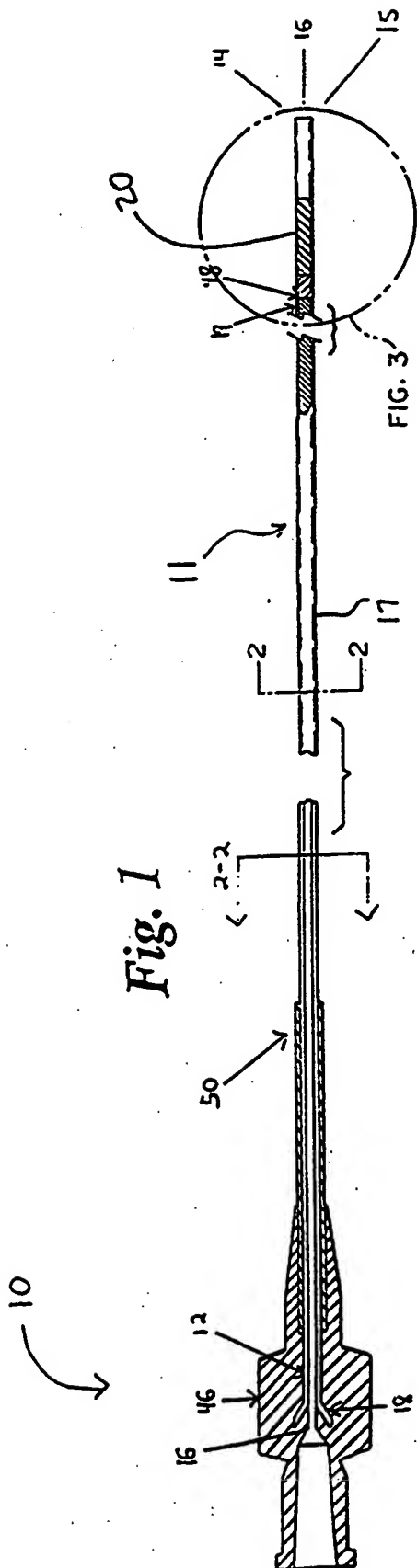


FIG. 3

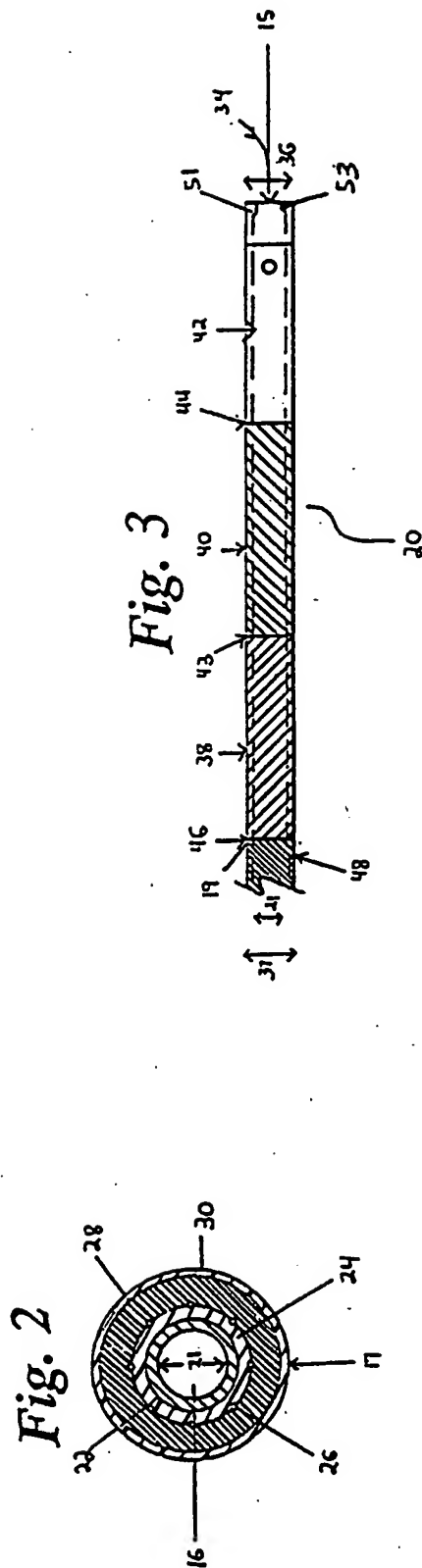
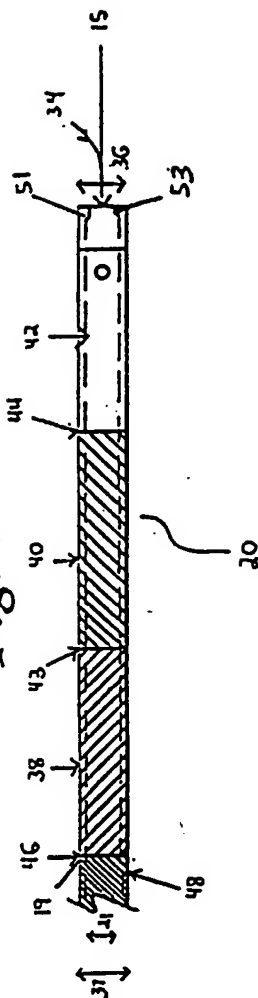


Fig. 3



Lung Volumes before and after Lung Volume Reduction Surgery

Quantitative CT Analysis

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The volume and severity of pulmonary emphysema in individual lungs were measured by means of quantitative computed tomography (CT) studies in 28 patients (14 women, 14 men, median age 65 yr) who underwent either bilateral ($n = 15$) or unilateral ($n = 13$) lung volume reduction surgery (LVRS). Spirometric, total body plethysmographic, and CT data (at TLC and RV) were correlated before and after LVRS. Lung volumes determined by CT correlated well with volumes obtained by total body plethysmography ($p < 0.0001$). For individual lungs after LVRS, CT-derived mean lung capacity decreased 13% and residual volume 20% ($p < 0.00001$ for each), while mean total functional lung volume (TFLV, defined as the volume of lung with CT attenuation greater than -910 Hounsfield units) increased 9% ($p < 0.01$), and the mean ratio of the air space to tissue space volume (V_{AS}/V_{TS}) decreased more at RV (23%) than at TLC (14%) ($p < 0.0005$ for each). In contrast, unilateral LVRS did not affect exhalation from the unoperated lung (2% reduction in RV, $p = NS$). The magnitude of the postoperative response (CT-derived TLC, RV, TFLV, V_{AS}/V_{TS}) of each operated lung was comparable for unilateral and bilateral LVRS. Thus, a lung's response to LVRS was independent from that of the contralateral lung. Moreover, postoperative alterations in TFLV and FEV_1 correlated significantly ($r = 0.80$, $p < 0.0001$), which suggests that the expansion of functioning tissue may contribute to the mechanism by which LVRS palliates airway obstruction. **Becker MD, Berkmen YM, Austin JHM, Mun IK, Romney BM, Rozenshtein A, Jellen PA, Yip CK, Thomashow B, Ginsburg ME. Lung volumes before and after lung volume reduction surgery: quantitative CT analysis.**

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Lung volume reduction surgery (LVRS) is a palliative treatment for the breathlessness of severe pulmonary emphysema (1). The goal of the operation is to remove 20 to 30% of the lung volume, preferably targeting the regions of most severe emphysema, while preserving lung tissue that is not severely diseased (2-4).

Because the definition of pulmonary emphysema is based on the anatomic demonstration of destruction of lung tissue, computed tomography (CT) is an imaging modality that is well suited for the *in vivo* study of emphysema (5-12). CT detects emphysema with a greater sensitivity than functional tests and can accurately quantify pulmonary emphysema (6-9). Functional correlates of CT in pulmonary emphysema are well established (FEV_1 , FEV_1/FVC ratio, FRC and DL_{CO}) (10-13). CT can also estimate accurately the total volume and weight of the two lungs combined, as well as the contraction and expansion of regional lung (8, 11).

In our institution, CT has been used since 1995 in both the preoperative evaluation of candidates for LVRS and in the

postoperative assessment of the results. We reviewed our experience retrospectively to compare the accuracy of lung volumes measured by CT and total body plethysmography, to analyze volume changes of individual lungs, to investigate the relation between postoperative improvement in airway obstruction with changes in lung volume and CT densitometry, and to compare the results of bilateral and unilateral LVRS.

METHODS

Between February, 1995, and June, 1996, 93 patients with diffusely confluent, severe pulmonary emphysema (mean % predicted FEV_1 $23 \pm 5\%$; mean % predicted DL_{CO} $30 \pm 14\%$) underwent lung volume reduction surgery (LVRS) (1, 2, 14) at our institution. Patients were excluded if they had CT evidence of bronchiectasis or giant bullae. Each of the 93 patients had a history of heavy cigarette smoking. Ventilation/perfusion lung scans were performed in each patient and revealed a heterogeneous distribution of disease, including zones ("target areas") of absent or minimal perfusion, matched by decreased ventilation. CT scans of the chest were obtained for each patient. Twenty-eight patients (14 women, 14 men, 49-75 yr old), each of whom underwent a postoperative CT scan (median 6.7 mo, range 3.2-8.4 mo) but were otherwise randomly selected, were included in the study. Both the study subgroup and the entire LVRS group each included a single patient with α -1-antitrypsin deficiency (also a heavy smoker). Fifteen patients had bilateral LVRS and thirteen patients had unilateral LVRS, which provided a total of 56 individual lungs (43 operated and 13 unoperated) for study.

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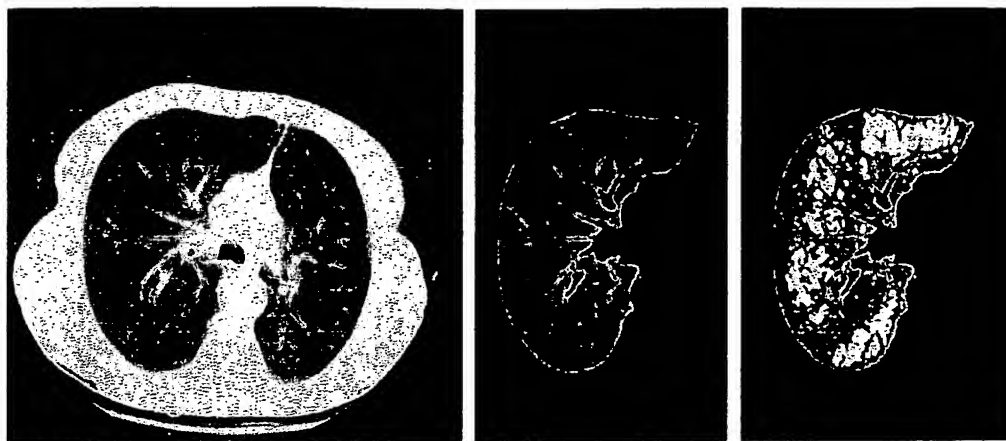


Figure 1. Computerized segmentation of a CT scan image. Original CT scan image (*left panel*). Isolation of the right lung (*middle panel*). Separation of the right lung into severely emphysematous and functioning regions using a CT attenuation threshold of -910 HU (*right panel*). The fraction of lung volume that is severely emphysematous (denoted in *white*) is defined to be the EI, while the remaining regions represent the TFLV (see METHODS).

CT Scans

Twenty-five preoperative and five postoperative CT scans were performed on the same conventional scanner (GE 9800 HiLite; GE Medical Systems, Milwaukee, WI), using contiguous sections, 10-mm collimation and the standard reconstruction algorithm. Three preoperative and 23 postoperative CT scans were performed by the same helical scanner (Somatom 4 Plus; Siemens, Erlangen, Germany) using a pitch of 1, 10-mm collimation, and the standard reconstruction algorithm. Each CT scan included a complete examination of the chest at both TLC and RV. If the patient had difficulty with breath-holding during the acquisition of a helical series, the examination was obtained in two increments. Intermittent rest periods were allowed during conventional scanning to combat patient fatigue. Intravenous contrast medium was not used.

The unwindowed CT images were transferred to a personal computer for an analysis that used custom software written in Visual C++ (Microsoft, Redmond, WA). Each CT scan image was analyzed twice by a seeded, region-growing algorithm (8, 13, 15). In this algorithm, the operator designates a region that consists of a single voxel that is within a lung, then the computer iteratively assesses the adjacent voxels, and those within a range of -500 to $-1,024$ HU are incorporated into the region. The region continues to grow outward until the point at which no adjacent voxels are within the acceptable range (e.g., all adjacent voxels are chest wall, anterior junction line, bronchus or mediastinum). Occasionally, the boundaries of the trachea, main bronchi and the anterior junction line had to be demarcated manually prior to employing the region-growing algorithm. First, the algorithm was used to isolate the right lung (Figure 1), then repeated to isolate the left lung. After an individual lung was isolated within an image, its volume and the distribution of CT attenuations (Figure 2) were recorded. Following the analysis of all images, the individual lung data were tabulated to give five parameters: individual lung total capacity (TLC_{IL}), individual lung residual volume (RV_{IL}), total functional lung volume (TFLV), an emphysema index (EI), and the ratio of the air space volume (V_{AS}) to the tissue space volume (V_{TS}).

TLC_{IL} and RV_{IL}

The air space and tissue space volumes of an individual lung are related to the CT-derived volume of an individual lung (V_{IL}) by the following relations (16):

$$V_{AS} = (\text{mean CT attenuation} / -1,000) \times V_{IL} \quad (1)$$

$$V_{TS} = V_{IL} - V_{AS} \quad (2)$$

Equation 1 is based on the assumption that the CT attenuations of air and lung tissue are $-1,000$ HU and 0 HU, respectively. Errors introduced into V_{AS} by deviations from these ideal attenuation values are small (unpublished result).

V_{AS} obtained at TLC is the total capacity for an individual lung (TLC_{IL}). The sum of the TLC_{IL} for each of the two lungs corresponds to the TLC. Similarly, V_{AS} obtained at RV is the RV_{IL} . The sum of the RV_{IL} for each of the two lungs corresponds to the RV.

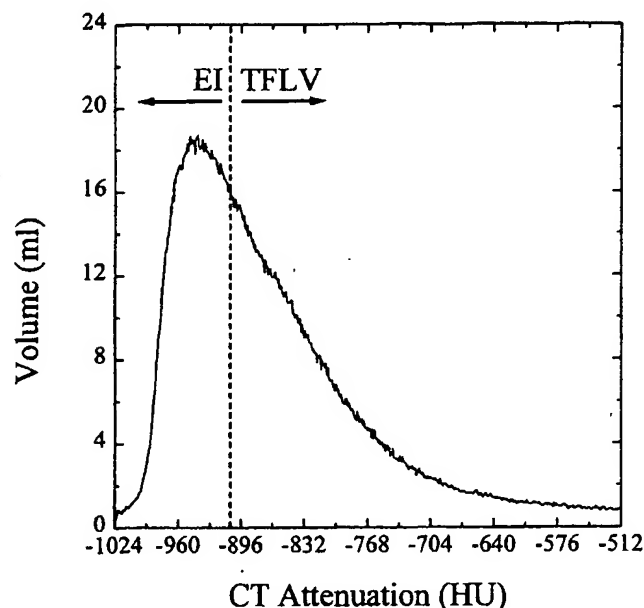


Figure 2. The distribution of CT attenuations for the right lung presented in Figure 1 (*center panel*). The vertical dashed line is the -910 HU threshold used to construct the EI and the TFLV (see METHODS). The fraction of pixels with CT attenuations below -910 HU (colored *white* in the *right panel* of Figure 1) is defined to be the EI. The area under the curve with attenuations above or equal to -910 HU is defined as the TFLV.

TABLE 1
CLINICAL PARAMETERS FOR THE STUDY SUBPOPULATION (n = 28 SUBJECTS)
AND ENTIRE LVRS POPULATION (n = 93 SUBJECTS)

	Study Subgroup	Entire LVRS Group	p Value
Mean age, yr	65 ± 7	65 ± 7	0.69
Age range, yr	(49–75)	(45–79)	
Gender			
Female	14	50	0.73
Male	14	43	
Type of LVRS			
Unilateral	13	26	0.07
Bilateral	15	67	
Mean FEV ₁ , % predicted			
Preoperative	22 ± 1	23 ± 1	0.67
Postoperative	29 ± 2	32 ± 1	0.91
6-min walk distance, feet			
Preoperative	721 ± 81	712 ± 44	0.91
Postoperative	959 ± 78	1,018 ± 57	0.53
Dyspnea Index, scale 0 to 5			
Preoperative	3.7 ± 0.2	3.8 ± 0.1	0.68
Postoperative	1.4 ± 0.2	1.6 ± 0.1	0.27

Values reported as mean ± SEM.

Emphysema Index

Emphysema Index (EI) has been defined as that percentage of a lung's volume that has CT attenuations less than the threshold of -910 HU, which has been shown to be the optimal threshold for 10 mm collimation (5, 13, 15, 17). This parameter is defined only at TLC. The calculation of this parameter is illustrated in Figures 1 and 2.

Air-to-Tissue Ratio

V_{AS}/V_{TS} is a measure of overall inflation and is calculated from Equations 1 and 2. Deviations of the air and lung tissue CT attenuations

from -1,000 HU and 0 HU, respectively, introduce only small errors into V_{AS}/V_{TS} (unpublished results).

TFLV and a CT Scan-Based Prediction of Postoperative FEV₁

Because the EI is that fraction of the lung that is most severely destroyed and poorly functioning, the volume of the remaining lung (with CT attenuations between -500 and -910 HU) represents the "total functional lung volume" (TFLV), i.e., the volume of lung that is relatively less destroyed and therefore most responsible for respira-

TABLE 2
PRE- AND POSTOPERATIVE CT FINDINGS IN 28 PATIENTS UNDERGOING LUNG
VOLUME REDUCTION SURGERY FOR SEVERE PULMONARY EMPHYSEMA

	Preoperative	Postoperative	Change	p Value
Individual operated lungs, n = 43				
Individual lung capacities, L				
RV _L	2.84 ± 0.12	2.30 ± 0.13	-20%*	0.00001
TLC _L	3.33 ± 0.13	2.95 ± 0.14	-13%*	0.00001
RV _L /TLC _L	0.87 ± 0.07	0.78 ± 0.12	-10%	0.00001
Total functional lung volume, L [†]	1.41 ± 0.07	1.54 ± 0.07	+9%	0.01
Individual lung EI, % [‡]	55 ± 2	46 ± 2	-16%	0.00001
V_{AS}/V_{TS}				
TLC	8.34 ± 0.29	7.10 ± 0.19	-14% [†]	0.0002
RV	7.53 ± 0.32	5.77 ± 0.20	-23% [†]	0.00001
Individual unoperated lungs, n = 13				
Individual lung capacities, L				
RV _L	2.42 ± 0.21	2.36 ± 0.20	-2%	0.51
TLC _L	2.97 ± 0.25	3.25 ± 0.27	+9%	0.0002
RV _L /TLC _L	0.84 ± 0.04	0.75 ± 0.07	-9%	0.0001
Total functional lung volume, L [†]	1.53 ± 0.17	1.56 ± 0.15	+2%	0.59
Individual lung EI, % [‡]	49 ± 5	52 ± 6	+6%	0.16
V_{AS}/V_{TS}				
TLC	7.60 ± 0.39	7.84 ± 0.31	+3%	0.49
RV	6.58 ± 0.34	6.19 ± 0.33	-6%	0.19

Definition of abbreviations: TLC_L = total capacity of an individual lung; RV_L = residual volume of an individual lung; TFLV = total functional lung volume (volume of lung with CT attenuation between -500 and -910 HU); EI = emphysema index (percentage of lung with CT attenuation < -910 HU); V_{AS}/V_{TS} = ratio of air space volume to tissue space volume.

Values reported as mean ± SEM.

* The absolute and relative (%) magnitudes of the reduction in RV_L were greater than the reduction in TLC_L (p < 0.0008 and p < 0.0001, respectively).

[†] The absolute and relative (%) magnitudes of the reduction in the V_{AS}/V_{TS} were greater at RV than at TLC (p < 0.0004 and p < 0.002, respectively).

[‡] Defined at TLC.

tory function (13, 15). TFLV is defined only at TLC. The calculation of this parameter is illustrated in Figures 1 and 2. A linear relation has been described between the TFLV and the FEV₁ (13). We have used this relation to predict postoperative FEV₁ from CT-calculated preoperative (preop) and postoperative (postop) TFLV, by the following equation:

$$\text{postop FEV}_1 = \text{preop FEV}_1 \times (\text{postop TFLV/preop TFLV}) \quad (3)$$

In this equation, TFLV is the sum of the TFLV from both lungs because they both contribute to the FEV₁.

Pulmonary Function Tests

Pre- and postoperative (6 mo) spirometric (Warren E. Collins, Inc., Braintree, MA) (FEV₁) and total body plethysmographic (Sensor-Medics Corp., Yorba Linda, CA) (TLC and RV) studies were available for 26 patients preoperatively and 27 patients postoperatively. The 6-min walk test was also performed and was available for 26 patients preoperatively and 27 patients postoperatively.

Dyspnea Index

Patients subjectively classified their degree of dyspnea pre- and postoperatively (6 mo) according to a 0–5 scale (18).

Data Analysis

Because plethysmography was available for 26 patients preoperatively and 27 patients postoperatively, plethysmography provided a total of 53 TLC and 53 RV measurements (including both pre- and postoperative values). Complete pre- and postoperative CT examinations were obtained on all 28 patients, but the postoperative CT images obtained at RV from two examinations were not available for computer analysis. Thus, CT provided pre- and postoperative TLC_{IL} for 56 individual lungs and RV_{IL} for 54 individual lungs. In order to compare CT with plethysmography, we added together either the CT-derived TLC_{IL} or the RV_{IL} from the individual right and left lungs to calculate the CT-derived overall TLC and RV, respectively.

CT versus plethysmography plots were constructed for the TLC, RV, VC (assessed as TLC–RV) and RV/TLC ratio, using Excel (Microsoft). Each plot contained both pre- and postoperative measurements. Corresponding pairs of CT and plethysmographic volumes were available for 53 TLC (26 pre- and 27 postoperative) and 49 RV, VC, and RV/TLC ratio (25 pre- and 24 postoperative) measurements.

Statistical Analysis

All statistical calculations were performed using Excel (Microsoft). The comparison of the study subgroup with the entire LVRS group (Table 1) was performed using either unpaired Student's *t* tests (age,

FEV₁, 6-min walk distance, dyspnea index) or χ^2 -tests (gender, type of LVRS). The pre- and postoperative CT parameters in Table 2 were compared using paired Student's *t* tests. The comparisons of unilateral and bilateral LVRS in Table 3 were performed using unpaired Student's *t* tests. Pearson's correlation coefficient (*r*) was used to compare the CT-derived and the plethysmographic lung volumes and the predicted (Equation 3) and measured postoperative FEV₁. The slope and intercept of the regression lines for the CT versus plethysmography plots (Figure 3) were compared with the line of identity by using Student's *t* tests with the null hypotheses that the slope is equal to 1 and that the intercept is equal to 0.

RESULTS

Comparison of the Study Subgroup with the Overall LVRS Group

The age and gender distribution, type of LVRS (unilateral or bilateral), pre- and postoperative FEV₁, 6-min walk distance and dyspnea index of the study subgroup were comparable to that of the overall LVRS group (Table 1).

Correlation between Imaging Methods and Plethysmography

TLC and RV calculated from CT correlated well with TLC and RV determined by plethysmography ($r = 0.90$ [$p < 0.0001$] and $r = 0.84$ [$p < 0.0001$], respectively) (Figure 3). The regression line for TLC, $y = 0.91x + 0.17$, was not significantly different from the line of identity (intercept: $p = 0.72$; slope: $p = 0.25$). The regression line for RV, $y = 0.75x + 1.66$, was significantly different from the line of identity (intercept: $p < 0.0001$; slope: $p < 0.01$). Comparison of the regression line for RV with the line of identity shows CT tended to overestimate RV (Figure 3).

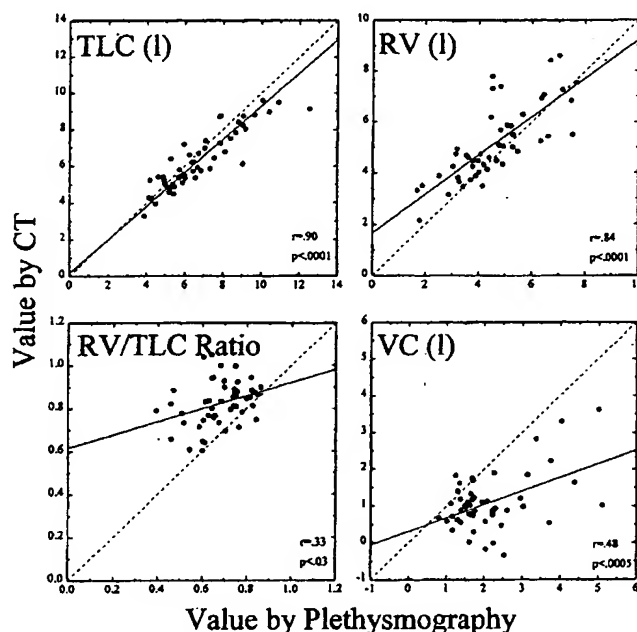


Figure 3. Correlation of CT-derived TLC, RV, VC, and RV/TLC ratio with plethysmographic findings. The regression lines are solid, while the line of identity is dashed. Notice that in two cases the CT-derived RV was actually greater than the corresponding CT-derived TLC, which resulted in two CT-derived VC values that were less than zero and two CT-derived RV/TLC values that were greater than one.

TABLE 3

UNILATERAL VERSUS BILATERAL LUNG VOLUME REDUCTION SURGERY: LACK OF A DIFFERENCE IN POSTOPERATIVE DECREASES IN TLC_{IL}, RV_{IL}, EI, AND V_{AS}/V_{TS} FOR OPERATED LUNGS

	Unilateral (n = 13)	Bilateral (n = 30)	p Value
TLC _{IL}	–15%*	–11%†	0.31
RV _{IL}	–25%*	–18%†	0.24
EI	–13%	–15%	0.81
V _{AS} /V _{TS} at TLC	–13%‡	–11%§	0.82
V _{AS} /V _{TS} at RV	–21%‡	–20%§	0.88

Definition of abbreviations: TLC_{IL} = total capacity of an individual lung; RV_{IL} = residual volume of an individual lung; EI = emphysema index (percentage of lung with CT attenuation < –910 HU); V_{AS}/V_{TS} = ratio of air space volume to tissue space volume.

* The absolute and relative (%) reductions in the magnitude of RV_{IL} were greater than the reduction in TLC_{IL} ($p < 0.004$ and $p < 0.0001$, respectively) for unilateral LVRS.

† The absolute and relative (%) reductions in the magnitude of RV_{IL} were greater than the reduction in TLC_{IL} ($p < 0.02$ and $p < 0.002$, respectively) for bilateral LVRS.

‡ The absolute and relative (%) reductions in V_{AS}/V_{TS} were greater at RV than at TLC ($p < 0.02$ and $p < 0.0006$, respectively) for unilateral LVRS.

§ The absolute and relative (%) reductions in V_{AS}/V_{TS} were greater at RV than at TLC ($p < 0.005$ and $p < 0.0008$, respectively) for bilateral LVRS.

In contradistinction to the TLC and RV measurements, two other CT-derived parameters, the VC and the RV/TLC ratio, correlated significantly but only modestly with plethysmographic results ($r = 0.48$ [$p < 0.0005$] and $r = 0.33$ [$p < 0.03$], respectively) (Figure 3). The slope of the regression line for VC, $y = 0.37x + 0.33$, was significantly different from the line of identity, while the intercept was not different (slope: $p < 0.0001$; intercept: $p = 0.18$). The intercept of the regression line for RV/TLC, $y = 0.30x + 0.62$, was significantly different from that of the line of identity, while the slope was not different (intercept: $p < 0.0001$; slope: $p = 0.72$). Comparison of the regression lines for VC and RV/TLC with the line of identity shows CT tended to underestimate VC and overestimate RV/TLC (Figure 3).

Pre- and Postoperative Lung Capacity

LQRS significantly reduced the TLC_{IL} (13%; $p < 0.00001$) and the RV_{IL} (20%; $p < 0.00001$) of operated lungs (Table 2). The absolute and relative (%) magnitude of this reduction was significantly greater at RV_{IL} than at TLC_{IL} ($p < 0.0008$ and $p < 0.0001$, respectively) (Table 2).

LQRS did not alter the RV_{IL} of unoperated lungs (Table 2). However, TLC_{IL} of unoperated lungs increased by 9% ($p < 0.0002$), so those lungs expanded postoperatively at end-inspiration.

Pre- and Postoperative TFLV and Predicted Postoperative FEV_1

On average, LQRS diminished the operated lung's TLC_{IL} by 13% ($p < 0.00001$), but the TFLV actually increased by 9% ($p < 0.01$) (Table 2). The TFLV for pre- and postoperative scans together with the preoperative FEV_1 allowed the postoperative FEV_1 to be predicted moderately well, using Equation 3 ($r = 0.80$, $p < 0.0001$, $n = 27$; Figure 4).

Pre- and Postoperative CT Attenuation and Disease Severity

For individual operated lungs, LQRS decreased significantly the RV_{IL}/TLC_{IL} (10%; $p < 0.00001$), EI (16%; $p < 0.00001$), and the V_{AS}/V_{TS} at both TLC and RV (14%, $p < 0.0002$, and 23%, $p < 0.00001$, respectively) (Table 2). The absolute and relative (%) magnitude of this reduction in the V_{AS}/V_{TS} was significantly greater at RV than at TLC ($p < 0.0004$ and $p < 0.002$, respectively) (Table 2). In contrast, LQRS did not alter significantly the EI or the V_{AS}/V_{TS} of the unoperated lungs (Table 2). However, LQRS significantly decreased the RV_{IL}/TLC_{IL} of unoperated lungs (9%; $p < 0.00001$).

Pre- and Postoperative FEV_1/VC

By plethysmography, FEV_1/VC was 0.32 ± 0.07 preoperatively and 0.33 ± 0.12 postoperatively ($p = 0.87$). The FEV_1/VC (% predicted) was 44 ± 9 preoperatively and 45 ± 14 postoperatively ($p = 0.67$).

Unilateral Versus Bilateral LQRS

The relative reductions in the TLC_{IL} , RV_{IL} , EI, and V_{AS}/V_{TS} (at both TLC and RV) for individual operated lungs after either unilateral or bilateral LQRS were not different statistically (Table 3). The absolute and relative (%) magnitude of the reduction in RV_{IL} was significantly greater than the reduction in TLC_{IL} for both unilateral and bilateral LQRS (Table 3). The absolute and relative (%) magnitude of the reduction in the V_{AS}/V_{TS} was significantly greater at RV than at TLC for both unilateral and bilateral LQRS (Table 3).

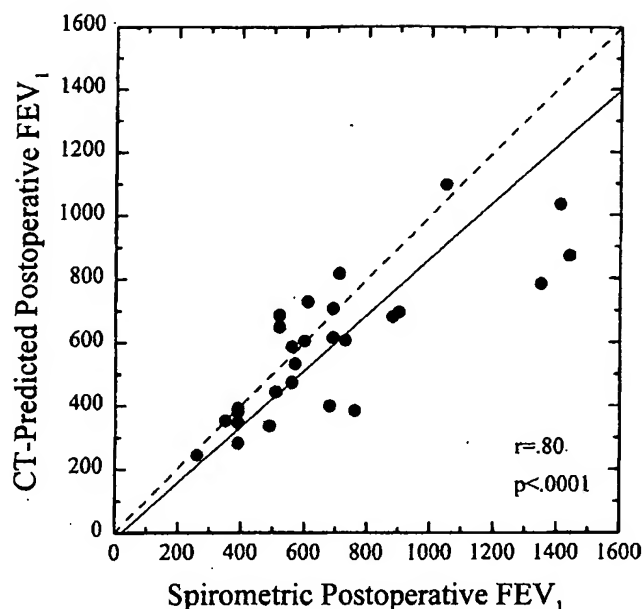


Figure 4. Correlation of CT-derived predicted postoperative FEV_1 with spirometric postoperative FEV_1 . The CT prediction of postoperative FEV_1 is determined by the preoperative FEV_1 multiplied by the ratio of postoperative to preoperative total functional lung volume, as determined by CT (METHODS, Equation 3). The regression line is solid, while the line of identity is dashed.

DISCUSSION

LQRS has a low mortality and morbidity (2, 14, 19, 20) and it frequently offers immediate postoperative relief from disabling respiratory insufficiency. The present study confirms that the beneficial result of surgery is probably due to the synergistic effect of multiple factors (21).

Reduced Air Trapping and Hyperinflation

Prior studies have shown that LQRS significantly reduces hyperinflation of the lung and air trapping, as evidenced by decreases in TLC and FRC (1, 3, 15, 22–24). The present study shows that LQRS reduced the volume of individual lungs at TLC_{IL} and at RV_{IL} (Table 2). Moreover, LQRS reduced air trapping in individual operated lungs, because RV_{IL}/TLC_{IL} was reduced postoperatively (Table 2). The fact that LQRS increased the fraction of gas exhaled from individual lungs is further supported by three additional results. First, the absolute and relative (%) magnitude of the average reduction in RV_{IL} was greater than the reduction in TLC_{IL} (Table 2). Second, the postoperative reduction in the V_{AS}/V_{TS} ratio was greater at RV than it was at TLC (Table 2). Third, because the severity of pulmonary emphysema correlates significantly with the RV/TLC (25), the postoperative reduction in the CT-derived emphysema index (EI) in the present study confirms that LQRS reduced the RV/TLC ratio, and thus reduced air trapping.

After LQRS, the remaining lung parenchyma must stretch to fill the available intrathoracic space. If there were no postoperative remodeling of the chest wall, then pleural pressure would be more negative due to the increased recoil of the remaining lung. Thus, the CT attenuation of at least some lung units can be expected to decrease. It follows that V_{AS}/V_{TS} (Equation 1) and EI each can be expected to have a compo-

ment tending to increase their postoperative values. Conversely, the preferential resection of severely emphysematous tissue can be expected to increase a lung's CT attenuation and to reduce both V_{AS}/V_{TS} and EI. The observed postoperative reduction in the V_{AS}/V_{TS} and EI (Table 2) shows that the latter factor predominated. The preferential excision of the most severely emphysematous tissues, which tend to retain air during expiration, presumably reduced RV. However, the postoperative increase in TFLV indicates that there was an expansion of lung and perhaps airways in the remaining lung. Furthermore, since TFLV is defined as lung with CT attenuation greater than -910 HU, this postoperative expansion involved the relatively less diseased tissues, which are expected to make an important contribution to the patient's respiratory function.

It must be noted that a reduction in the RV_{IL}/TLC_{IL} does not always imply a reduction in the volume of trapped gas. For example, LVRS reduced RV_{IL}/TLC_{IL} of the unoperated lungs (Table 2). However, in contrast to the operated lungs, this effect was the result of postoperative increases in TLC_{IL} , while the RV_{IL} was unaltered (Table 2).

Reduced Obstruction to Airflow

The original concept of LVRS, as proposed by Brantigan and colleagues (27), was based on the theory that decreased elastic traction on the airways increases airway obstruction and that surgical reduction of lung volume helps restore this elastic traction. Indeed, Gelb and coworkers (22, 26) demonstrated an increase in the slope of the maximum flow-static recoil curve during forced expiration. These findings are consistent with the concept of dilation of airways following LVRS.

We failed to find a change in the FEV_1/VC following LVRS. This result could be interpreted as demonstrating proportional expansion of airways as well as airspace volume in the remaining lung. However, caution is urged in using CT-measured volume data alone to determine the mechanisms limiting maximum expiratory flow in these patients. The situation may be quite complex because a number of competing factors determine the net effect of LVRS on FEV_1 . For example, the surgical removal of functioning airways can be expected to decrease FEV_1 , while increased recoil can be expected to have the opposite effect.

Unilateral Versus Bilateral LVRS

Comparison of the effect of LVRS on the volume of each lung in the individual patient provides evidence that the beneficial effects of LVRS are due to the surgical alterations in lung morphology, and that these surgical alterations affect each lung independently.

Our results support the results of Cooper and associates who found that the benefit derived from LVRS is in fact due to the operative procedure and cannot be explained solely by the effects of preoperative medical management and exercise rehabilitation (2). After unilateral LVRS, the operated lungs improved their ability to exhale (as evidenced by reductions in lung volume and V_{AS}/V_{TS} that were greater at RV than at TLC), while the ability of unoperated lungs to exhale was not altered (Tables 2 and 3). Thus, a patient's enhanced ability to exhale after unilateral LVRS was localized to the operated lung, while the unoperated lung makes no contribution to the postoperative improvement. Moreover, postoperative improvements in FEV_1 correlated with increased TFLV (Figure 4), but TFLV was altered only in operated lungs (Table 2). Therefore, postoperative improvements in FEV_1 after unilateral LVRS appear to localize to the operated lung.

Two aspects of our results indicate that the response of an individual lung to LVRS is independent of the response of the contralateral lung, whether operated or unoperated. First, there was no significant difference between the relative magnitude of the response of individual operated lungs (as measured by postoperative alterations in TLC_{IL} , RV_{IL} , EI and V_{AS}/V_{TS}) to either unilateral or bilateral LVRS (Table 3). Thus, for example, the postoperative expansion (mean 9% at TLC) of the unoperated lung in unilateral LVRS did not affect the magnitude of the volume reduction in the contralateral lung (Table 2). Second, the reduction in volume and in V_{AS}/V_{TS} of the operated lungs was greater at RV than at TLC after either unilateral or bilateral LVRS (Table 3). So, in either instance, the operated lungs were not just smaller, but they were also able to expel a higher fraction of gas than they did preoperatively.

In the case of unilateral LVRS, reduction in the operated lung's volume led to an increase in volume of the contralateral unoperated lung at TLC. On average, the volume expansion of the unoperated lung was approximately 70% of the volume reduction of the operated lung (Table 2). This result suggests the presence of interdependence between the hemithoraces. Presumably, the degree of interdependence is a function of the compliance of the lungs as well as that of the mediastinum. It should be noted that the residual volume of the unoperated lungs was unchanged after unilateral LVRS (Table 2). Thus, although unoperated lungs at TLC_{IL} were larger postoperatively than preoperatively, the ability of the patient to expel gas from them was not diminished.

Short- and long-term results after bilateral LVRS have been shown to be better than after unilateral LVRS (2, 4, 28). Our data provide imaging evidence that bilateral LVRS is superior to unilateral LVRS simply because it provides a larger volume reduction. If the distribution of emphysema is much more severe in one lung than the other, or if bilateral LVRS is inadvisable, unilateral LVRS remains an effective alternative because it reduces volume and increases the patient's ability to exhale, albeit less than after bilateral LVRS.

In the present series, CT-derived TLC and RV were shown to compare favorably with plethysmographic TLC and RV. This result implies that CT also accurately measured individual lung volumes (TLC_{IL} and RV_{IL}). Differences between volumes measured by plethysmography and CT are likely due to the combination of several factors: (1) conventional CT requires repetitive, prolonged breath holding that often fatigues these severely dyspneic patients; (2) variations in the method and vigor with which a patient was coached for the two types of examination; and (3) dependency of lung volume upon position (supine versus sitting) (29). An additional, presumably minor, factor contributing to the discrepancy between lung volumes measured by CT and those measured by plethysmography is that only the latter includes the volume of gas in the trachea and the main bronchi. We believe that the correlation between our CT and plethysmographic findings show that these considerations introduced relatively small errors into the TLC_{IL} and RV_{IL} , while the errors in VC and RV_{IL}/TLC_{IL} were larger. Also, most of our analysis is based on the relative (%) postoperative alterations in the various CT parameters rather than their absolute values, so systematic errors may tend to cancel out.

A potential limitation of the present study is that two different CT scanners were utilized, so the differences in CT attenuation that we have interpreted as caused by the operative procedure may instead represent technical differences between scanners. We believe, however, that effects, if any, of this difference were minimal because attenuation data ob-

tained by scanners of different leading manufacturers have been shown to be virtually identical (30).

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Lung Volume Reduction Surgery Alters Management of Pulmonary Nodules in Patients With Severe COPD*

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Objective: To examine the role of lung volume reduction surgery (LVRS) in expanding the treatment options for patients with single pulmonary nodules and emphysema.

Methods: Retrospective review of all patients undergoing LVRS at the University of Michigan between January 1995 and June 1996. Those undergoing simultaneous LVRS and resection of a suspected pulmonary malignancy formed the study group and underwent history and physical examination, pulmonary function tests, chest radiography, and high-resolution CT of the chest. If heterogeneous emphysema was found, cardiac imaging and single-photon emission CT perfusion lung scanning were performed. All study patients participated in pulmonary rehabilitation preoperatively. Age- and sex-matched patients who had undergone standard lobectomy for removal of pulmonary malignancy during the same period formed the control group.

Results: Of 75 patients who underwent LVRS, 11 had simultaneous resection of a pulmonary nodule. In 10 patients, the nodules were radiographically apparent with 1 demonstrating central calcification. Histologic evaluation revealed six granulomas, two hamartomas, and three neoplastic lesions (one adenocarcinoma, one squamous cell, and one large cell carcinoma). Preoperative FEV₁ was 26.18±2.49% predicted in the LVRS group and 81.36±6.07% predicted (p=0.000001) in the control group, and the FVC was 65.27±5.17% predicted vs 92.18±5.53% predicted (p=0.002). Two LVRS patients had a PaCO₂ >45 mm Hg while 11 exhibited oxygen desaturation during a 6-min walk test. Postoperative complications occurred in two LVRS patients and three control patients. The mean length of stay in the LVRS group (7.55±1.10 days) was not different than in the control group (8.81±1.56 days). Three months after LVRS and simultaneous nodule resection, FEV₁ rose by 47%, FVC by 25%, and all study patients noted less dyspnea as measured by transitional dyspnea index.

Conclusions: Simultaneous LVRS and resection of a suspected bronchogenic carcinoma is feasible and associated with minimal morbidity and significantly improved pulmonary function and dyspnea.

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Key words: lung cancer; lung volume reduction surgery; severe chronic airflow obstruction

Abbreviations: BDI=baseline dyspnea index; DCO=diffusion of carbon monoxide; HRCT=high-resolution CT; LVRS=lung volume reduction surgery; SPECT=single-photon emission CT; TDI=transitional dyspnea index

Pulmonary malignancy is the single most common cause of cancer death in both men and women in the United States. Most patients with bronchogenic carcinoma also have coexisting ob-

structive lung disease. In these individuals, the goal of management is to resect the malignancy without compromising respiratory function. Many investigators have sought to define the risks of pulmonary resection in individuals with suspected malignancy.¹ Recent recommendations have concluded that individuals with predicted postoperative FEV₁ <40% or diffusion of carbon monoxide (DCO) <40% predicted be considered at particularly high risk because of high morbidity and mortality.¹⁻³

The resurgence in lung volume reduction surgery (LVRS) has provided an additional surgical approach

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to improving short-term lung function and exercise capacity in individuals with advanced emphysema after bilateral⁴ and unilateral lung volume reduction.^{5,6}

We hypothesized that simultaneous LVRS and wedge resection of a single pulmonary malignancy could be performed successfully in patients who would otherwise be excluded from a potentially curative surgical approach. We report our experience with 11 such patients and demonstrate that combined LVRS and surgical resection of pulmonary nodules is feasible with minimal surgical morbidity and improved postoperative pulmonary function. This combined surgical technique expands the opportunities for surgical resection of suspected, malignant pulmonary nodules.

MATERIALS AND METHODS

Patient Selection

We reviewed the medical records of all patients who underwent LVRS at the University of Michigan Medical Center between January 1, 1995 and May 30, 1996. Both nodules identified during preoperative evaluation for LVRS and those identified at the time of surgery were included. Patients who underwent simultaneous LVRS and resection of the nodular density formed the study group. Study group patients were matched with individuals of the same age and sex who underwent standard lobectomy during the same time period by the same thoracic surgeon (R.W.) and who were selected by a review of the thoracic surgical records.

Preoperative Evaluation for LVRS

All patients underwent a detailed history and physical examination. Breathlessness was measured using the baseline/transitional dyspnea indexes (BDI/TDI) of Mahler et al.⁷ Routine laboratory data included CBC count, electrolytes, and liver function studies.

Pulmonary Function Testing: Spirometry and lung volumes were performed on a calibrated pneumotachograph (Medical Graphics Co.; St. Paul, Minn) and values were expressed as a percent of the predicted values published by Morris et al.⁸ Lung volumes were measured in a whole-body plethysmograph and the data were expressed as a percent of predicted values.⁹ Lung volumes were additionally measured using N₂ washout and expressed as a percent of predicted values.¹⁰ Maximum voluntary ventilation was measured in all subjects during a 12-s maneuver.

Six-minute walk distance was measured in an air-conditioned hall after standard instructions.¹¹ Supplemental oxygen was titrated to maintain an oxygen saturation above 88%. The distance the patient walked was measured in feet over 1-min intervals.

Chest Imaging: Standard chest radiographs and conventional and high-resolution CT (HRCT) were obtained on all patients. HRCT was performed with 1.0- or 1.5-mm-thick axial sections at 1-cm intervals throughout the entire thorax using a scanner (General Electric CT/T Advantage Scanner; Milwaukee) operating in axial nonhelical mode. No oral or IV contrast was administered. The distribution and severity of emphysema as well as the presence and location of additional findings were described by a single chest radiologist (E.A.K.).

Perfusion scans and single-photon emission CT (SPECT) imaging were performed following the IV injection of 4 mCi of ^{99m}Tc macroaggregated albumin. Eight planar views were obtained. Subsequently, SPECT images were acquired with a dual-head large field of view SPECT system, using 180° rotation per head, with at least 32 camera stops. These were reconstructed into transverse, coronal, and sagittal views and were displayed on computer.

Cardiac Imaging: Dobutamine echocardiography was routinely utilized. If right ventricular function appeared compromised or if pulmonary hypertension was suspected, an outpatient right-sided heart catheterization was performed. Similarly, if left ventricular wall motion abnormalities were noted during dobutamine infusion, an outpatient left-sided heart catheterization was performed.

Pulmonary Rehabilitation: All patients undergoing LVRS were required to complete at least 6 weeks of intensive pulmonary rehabilitation. Programs emphasized education and exercise training¹² with the latter including both lower and upper extremity conditioning.¹³ The pulmonary function data shown were obtained following completion of pulmonary rehabilitation.

Surgical Techniques

Surgical techniques for study patients included either median sternotomy with bilateral apical lung volume reduction utilizing a linear stapler buttressed with strips of bovine pericardium⁴ or unilateral lower lobe reduction via a muscle-sparing thoracotomy. The location and volume of resected tissue were guided by findings from HRCT and SPECT scanning that delineated those areas involved with severe emphysematous change receiving minimal, if any, perfusion. All nodules not contained within the parenchyma removed as a function of lung volume reduction were excised via minimal wedge resection. All patients undergoing wedge resection of carcinoma had a grossly complete resection of the tumor. Control patients had a standard lobectomy or bilobectomy via muscle-sparing thoracotomy. Pulmonary nodules and resected pulmonary parenchyma were submitted to the pathology department for permanent fixation with appropriate fungal staining techniques as indicated. While hospitalized, patients were followed up closely by both the pulmonary and thoracic surgery services.

Data Collection

Preoperatively, pulmonary function data, exercise testing, radiographic imaging, and assessment of dyspnea were obtained as noted in study patients. Control subjects underwent spirometric measurement only. Spirometric data were collected on all patients undergoing simultaneous LVRS and resection of suspected bronchogenic carcinoma at least 3 months postoperatively. Perioperatively, all minor and major complications, mortality, and length of hospital stay were recorded for both groups. All data are expressed as mean \pm SE.

Data Analysis

Comparison between study and control groups was made utilizing an unpaired, two-tailed Student's *t* test. A *p* value <0.05 was considered statistically significant.

RESULTS

From January 1995 to June 1996, 467 patients were evaluated for LVRS at the University of Mich-

igan Medical Center. Of these, 113 were deemed appropriate for surgery and 75 have undergone either unilateral (16 patients) or bilateral (59 patients) LVRS. Eleven patients were noted to have single pulmonary nodules, defined as a nodule measuring 2 cm, discovered preoperatively during routine radiographic imaging ($n=10$) or at the time of surgery ($n=1$). These patients underwent simultaneous LVRS and resection of the nodule. Patient characteristics and preoperative lung function for both the study and control groups are listed in Table 1. There was a significant difference in FEV₁ between the study and control groups ($26.18 \pm 2.49\%$ predicted compared with $81.36 \pm 6.07\%$ predicted) ($p=0.00001$). A similar difference was seen in FVC between study patients ($65.27 \pm 5.17\%$ predicted) and control patients ($92.18 \pm 5.53\%$ predicted) ($p=0.0002$) (data not shown). Preoperative 6-min walk distance in the study group was 540.00 ± 99.63 feet with all experiencing significant desaturation (lowest oxygen saturation, $88.6 \pm 1.24\%$).

Despite marked differences in preoperative pulmonary function, the mean length of stay did not differ significantly between the study and the control groups (7.55 ± 1.10 days compared with 8.81 ± 1.56 days) (Table 2). The characteristics and histologic diagnoses of the nodules resected in the study group patients are listed in Table 3. Of the two nodules in the study group with radiographic evidence of calcification, the pattern of calcification was consistent with a benign process in one. In the control group, the identity of the resected lesions included one carcinoid tumor, four squamous cell carcinomas, five adenocarcinomas, and one small cell carcinoma.

Table 2—Details of Surgical Intervention in Study and Control Groups*

Patient	Extent of Surgery	Length of Stay, d
Study group		
1	MST, RLL LVRS	12
2	(B) apical LVRS	7
3	(B) apical LVRS	6
4	MST, RLL LVRS	6
5	(B) apical LVRS	6
6	MST, LLL LVRS	16
7	(B) apical LVRS	4
8	(B) apical LVRS	5
9	(B) apical LVRS	4
10	MST, RLL LVRS	9
11	(B) apical LVRS	8
Mean		7.55 ± 1.10
Control group		
Mean	8 RUL, 3 LUL, 1 RML, 1 RLL [†]	8.81 ± 1.56

*MST=muscle-sparing thoracotomy; B=bilateral; RUL=right upper lobectomy; LUL=left upper lobectomy; RML=right middle lobectomy; LLL=left lower lobectomy; RLL=right lower lobectomy.

[†]Two patients underwent bilobectomies.

Four of the 11 patients required wedge resection of lung remote from the areas involved in LVRS in order to resect the nodules. Despite the removal of potentially functioning pulmonary parenchyma proximate to the nodules, these four patients still demonstrated significant improvement in postoperative pulmonary function. Figure 1 illustrates the preoperative HRCT of study group patient 2, demonstrating apical predominant bullous emphysema and the presence of a pulmonary nodule in the right upper lobe.

Table 1—Patient Characteristics*

Patient/Age, yr/Sex	FEV ₁ , L (% Predicted)	RV, L (% Predicted)	DCO, mL/mm Hg (% Predicted)	PaCO ₂ , mm Hg	PaO ₂ , mm Hg
Study group					
1/52/M	0.72 (19)	9.62 (388)	11.56 (36)	41	69
2/71/M	1.10 (34)	5.55 (203)	10.76 (39)	36	67
3/55/F	0.51 (22)	6.75 (466)	8.87 (41)	33	77
4/72/M	0.82 (29)	5.61 (241)	8.79 (35)	39	70
5/53/F	0.32 (14)	4.48 (327)	10.86 (51)	49	54
6/67/M	1.19 (37)	4.57 (181)	13.15 (48)	34	72
7/66/F	0.53 (24)	6.52 (400)	6.56 (30)	50	68
8/54/M	0.98 (26)	7.25 (297)	Not done	42	73
9/55/F	1.01 (39)	4.06 (251)	13.41 (58)	38	65
10/56/F	0.63 (28)	4.67 (320)	15.94 (74)	40	71
11/62/M	0.53 (16)	9.04 (372)	Not done	39	77
6M	0.76 ± 0.08	6.19 ± 0.53	11.10 ± 0.89	40.09 ± 1.56	69.36 ± 1.82
60.27 ± 2.17 5F	(26.18 ± 2.49)	(313.27 ± 25.57)	(45.78 ± 4.31)		
Control group					
60.27 ± 2.17 6M	2.33 ± 0.17	NA	NA	NA	NA
5F	(81.36 ± 6.07)				

*NA=not available; RV=residual volume.

Table 3—Nodule Characteristics*

Patient	Radiographically Apparent	Size, cm	Calcification	Location	Histologic Diagnosis
1	Yes	2.5	Yes	RLL	Granuloma
2	Yes	1.8	No	RUL	Large cell cancer
3	Yes	1.0	No	LLL	Hamartoma
4	Yes	2.4	No	RUL	Squamous cell cancer
5	Yes	0.5	No	RUL	Granuloma
6	No	NA	NA	LUL	Granuloma
7	Yes	1.5	No	LUL	Hamartoma
8	Yes	1.0	Yes	RUL	Granuloma
9	Yes	0.5	No	LUL	Granuloma
10	Yes	1.5	No	RLL	Adenocarcinoma
11	Yes	1.0	No	RLL	Anthracoic lymph node

*See Table 1 and 2 footnotes for explanation of abbreviations.

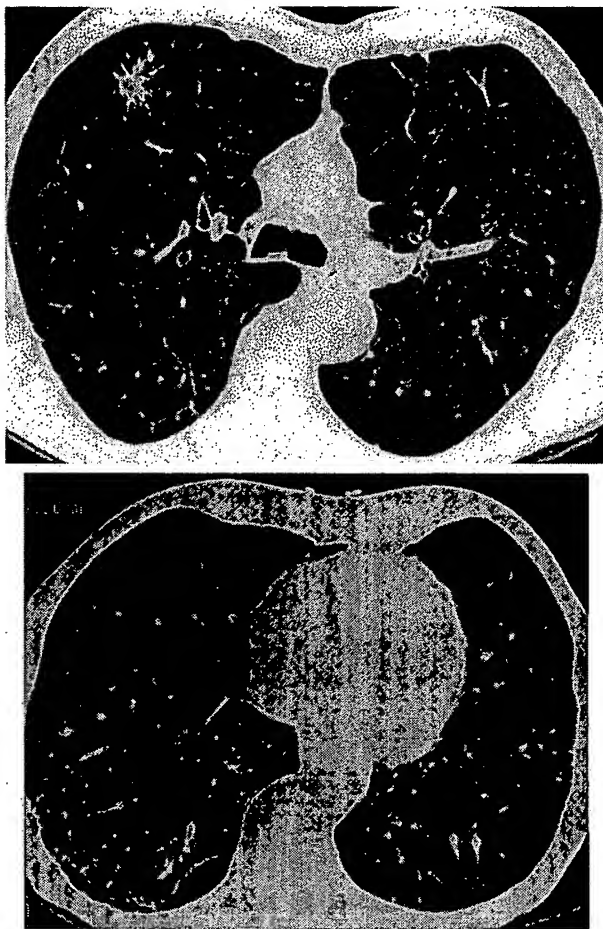


FIGURE 1. Preoperative HRCT of patient 2 prior to LVRS and wedge resection of pulmonary nodule demonstrating upper lobe predominant bullous emphysema and presence of a noncalcified right upper lobe pulmonary nodule (*top*) and relative sparing of the parenchyma of the bilateral lower lobes (*bottom*).

The postoperative mortality rate was 0% in the study and control groups. In addition, only two patients in the study group developed evidence of

significant morbidity. Patient 1 developed right middle lobe pneumonia and patient 5 had a prolonged air leak requiring continued chest tube use. In the control group, three patients developed postoperative complications. One patient had a wound infection necessitating surgical debridement and IV antibiotics and two other patients had prolonged air leaks (one with the additional complication of an infection at the site of the chest tube that required IV antibiotics). During follow-up, the mortality rate has remained 0% in both groups. Only LVRS patient 4 has required hospitalization, approximately 4 months after surgery, for community-acquired pneumonia.

Figure 2 illustrates the FEV₁ (percent predicted) and FVC (percent predicted) before and at least 3 months after surgery in the study group. A rise in FEV₁ is noted in all individuals. The mean rise in FEV₁ was 47% while the increase in FVC was 25%. Figure 3 illustrates the BDI and TDI in all subjects. There was significant preoperative breathlessness in most study patients, consistent with the presence of severe chronic airflow limitation. Importantly, all patients undergoing simultaneous LVRS and nodule resection noted improved breathlessness after surgery, as indicated by a positive TDI in all subjects.

Follow-up time ranged from 8 to 20 months (mean, 13 months). During this period of time, no patient with proved bronchogenic carcinoma has demonstrated evidence of recurrence.

DISCUSSION

We demonstrate the feasibility of combined LVRS and resection of solitary pulmonary nodules in 11 patients with very severe COPD. These individuals, who were considered to be at prohibitive risk using standard preoperative criteria, demonstrated no increase in hospital length of stay or hospital compli-

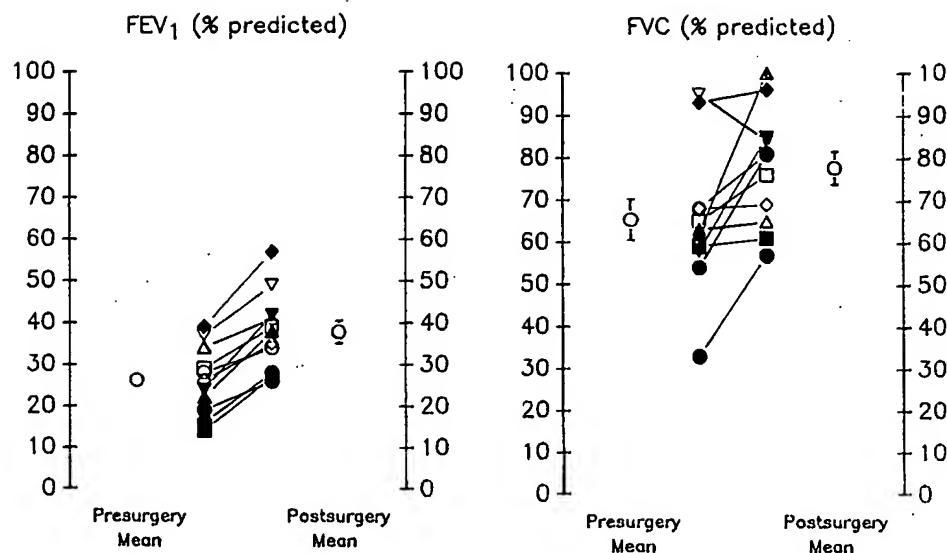


FIGURE 2. Comparison of FEV₁ and FVC as a percent of predicted values before (preoperative) and after surgery (postoperative) in 11 patients undergoing simultaneous LVRS and excision of a pulmonary nodule.

cations after undergoing simultaneous surgical excision of the pulmonary lesion and lung volume reduction. Furthermore, pulmonary function and dyspnea improved in all patients after surgery. Surgical criteria for operability of solitary pulmonary nodules must be updated in the era of LVRS.

Based on years of experience with pulmonary resection, extensive criteria have been developed to select patients with minimal risk for perioperative complications and postoperative respiratory insufficiency.^{1,14} The exclusionary criteria are listed in

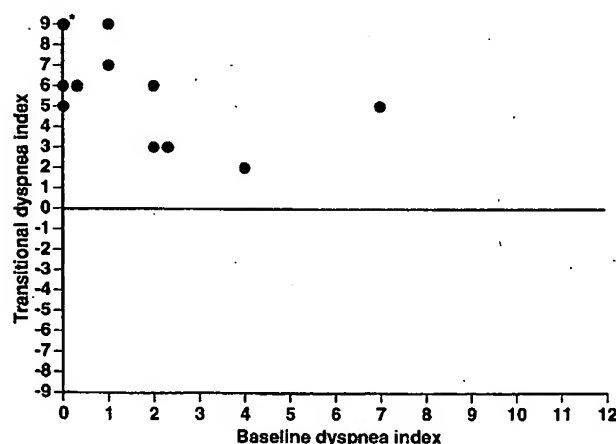


FIGURE 3. BDI plotted vs TDI in 11 patients undergoing simultaneous LVRS and excision of a pulmonary nodule. A positive value on the TDI axis indicates a lessening of dyspnea after LVRS. The higher the value, the greater the improvement in the level of dyspnea. On the BDI axis, a value of zero represents the most severe level of dyspnea. See text for greater detail. Asterisk=no BDI for this patient.

Table 4. Using criteria based upon the FEV₁,^{15,16} predicted postoperative FEV₁,^{2,14,17} predicted postoperative DCO,¹⁸ or maximum oxygen uptake on exercise testing,^{19,20} our patients would be considered at very high risk and would not generally have been offered surgical therapy for their lung nodules.

While previous investigators have documented the feasibility of limited resection in individuals with respiratory compromise,²¹⁻²⁵ most have provided limited data regarding selection criteria or postoperative response. Errett and colleagues²² noted little difference in perioperative course and postoperative outcome in individuals with moderate airflow obstruction (mean FEV₁ of 1.56 L). Miller and Hatcher²³ noted little perioperative difficulty in individuals with much more severe airflow obstruction (FEV₁ <1.0 L) but noted increased local recurrence²⁰ and advocated postoperative radiation therapy to minimize this risk. Neither group commented on postoperative pulmonary function or overall functional status. We document both gross anatomic resection of pulmonary nodules and a significant

Table 4—Standard Preoperative Exclusionary Criteria

Preoperative Criteria	No. of Patients Potentially Denied Surgery
FEV ₁ <0.6 L ¹⁶	4/11
FEV ₁ -ppo <40% predicted ²	11/11
DCO-ppo <40% predicted ²	4/9
PaCO ₂ >45 mm Hg ¹⁸	2/11
Desaturation with exercise (<89%) ²	11/11

*ppo=predicted postoperative value.

improvement in pulmonary function with increased overall functional status 3 months after surgery.

Importantly, the degree of postoperative complications was no different than in the matched control group with preserved pulmonary function. The smooth perioperative course was likely dependent on the aggressive, multidisciplinary treatment of these patients in the postoperative period, emphasizing pulmonary hygiene and adequate pain control. In addition, all study group patients had been rigorously screened preoperatively with active participation in pulmonary rehabilitation programs, including exercise training. Such a rigorous preoperative protocol was not used for the control group patients. Our study and control patients were matched for the months in which surgery took place and the length of stay for the control patients reflects the norm at our institution for this period. Recently, length of stay for both lobectomy and LVRS has decreased further.

While much of the improvement in lung function expected after LVRS appears gradually over the first several months after surgery,²⁶ there are recent data suggesting improved static elastic recoil pressure in the immediate postoperative period which could lead to early improvement in airflow characteristics and, therefore, could have simplified perioperative management.²⁷ Preliminary reports have suggested the possibility of combined lung volume reduction and cancer resection,^{28,29} although limited follow-up information was provided. To our knowledge, our series is one of the first to report impressive early results after LVRS and simultaneous resection of a suspected lung cancer and is the first to compare such results against those of a control group with essentially normal pulmonary function who had standard surgical procedure for resection of a known bronchogenic carcinoma. Recently reported was a series of 51 patients undergoing LVRS and resection of a suspicious pulmonary nodule.³⁰ Eleven of these patients were demonstrated to have non-small cell cancer and 40 had benign lesions. At the time the article was written, none of the patients with bronchogenic cancer had demonstrated evidence of recurrence and the postoperative complication rate was similar to that in our own series.

Despite our favorable short-term results, in terms of morbidity and mortality, the potential disadvantages of limited surgical resection for lung cancer³¹ remain an important drawback to the technique. While some reports comparing limited resection via segmentectomy vs lobectomy have demonstrated adequate postoperative morbidity and mortality with no significant difference in survival rates,^{22,24} a controlled study has confirmed a distinct increase in local recurrence and overall death rate (75% and 30%, respectively) with limited resection (segmen-

tectomy or wedge) compared to lobectomy.³² Although not subjected to a prospective comparison, limited resection appears to offer a survival advantage when compared to radiation therapy in stage I non-small cell lung cancer.³³ In addition, LVRS results in improved pulmonary function, while external-beam radiation may result in lost pulmonary function. It is possible that the improved pulmonary function attributable to LVRS may improve the ability of patients to tolerate postoperative radiation therapy in an attempt to minimize local recurrence.³⁴ In addition, combined LVRS and resection of a small bronchogenic carcinoma via median sternotomy does not allow a thorough hilar or mediastinal lymph node dissection. Thus, important prognostic information is lost when only a wedge resection is performed.

We emphasize that combined LVRS and wedge resection of pulmonary nodules is not appropriate for all patients with severe COPD and an indeterminate pulmonary nodule. Our results are applicable only to a highly select group of patients who underwent surgery primarily for emphysema, not the lung nodule. Our patients were selected for LVRS on the basis of severe airflow obstruction, hyperinflation, and the presence of identifiable hypoperfused or severely emphysematous portions of the lung, *ie*, "target zones." We believe that our successful results are, at least in part, due to the improved pulmonary function brought about by LVRS, and do not claim that successful pulmonary resection can be accomplished in all patients with severe COPD. The pulmonary nodules in our patients were identified as part of their evaluation for LVRS. However, based on our data, we believe it is feasible to evaluate patients with severe airflow limitation in the clinical scenario of a single pulmonary nodule with hopes of performing this dual procedure. Furthermore, our results indicate that the incidental discovery of a suspicious lung nodule during evaluation for LVRS need not be a contraindication to surgical therapy for emphysema.

In summary, our study demonstrates the feasibility of resecting localized pulmonary lesions in individuals with very severe COPD. Using an aggressive, multidisciplinary approach, including pulmonary rehabilitation, in a select group of patients, the hospital course was not significantly different from a group of low-risk individuals undergoing standard lobectomy for bronchogenic carcinoma. In addition, the improved lung function seen with simultaneous lung volume reduction is a clear advantage to alternative treatment modalities. Long-term follow-up is needed to better define the optimal role of simultaneous lung cancer resection and volume reduction in patients with advanced COPD.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

I. TWO NEW METHODS FOR DIRECT AND INDIRECT OBSERVATION.

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In recent papers we have endeavored to stress the importance of bronchial obstruction in various types of lung pathology. Fundamental researches on the relation of bronchial obstruction to pulmonary disease were done as far back as 1844 and 1846 by Mendelssohn¹ and Traube,² who obstructed the bronchi of animals with shot, paper and gum arabic and produced atelectasis. It remained, however, for Lichtheim,³ in 1879, to show that ligation of a bronchus is followed by absorption of the gases of the air and atelectasis, but that a combined ligature of the bronchus to a lobe and its corresponding pulmonary artery is not followed by atelectasis. This was the first definite demonstration that the blood circulation through the lung is an indispensable factor concerned with the absorption of gases in the alveoli. Moreover, under direct vision he observed the actual speeds of absorption of carbon dioxide, oxygen and nitrogen by the lung. The objection could be raised, and not without

* This work was aided by a gift of Mrs. John L. Given in support of Surgical Research and a grant from the National Research Council Fund.
† A complete bibliography will accompany the third and last paper of this series, "A Theory of Atelectasis."

justification, that some of the observations of Lichtheim are non-physiologic in the sense that the thoracic cavity had been opened during the course of the experiments.

We shall not attempt to discuss here the train of thought by which bronchial obstruction has been correlated with atelectasis, postoperative pneumonia, lobar pneumonia and other pathologic states of the lung. In our previous papers^{4,5,6,7,8,9,10} we endeavored to give a comprehensive history and view of the subject in general and of the special importance of bronchial obstruction in the pathogenesis of pulmonary disease.

More particularly controversy has waxed keen concerning the etiology of postoperative atelectasis. We believe it may conservatively be stated that at the present writing the only definitely proven direct etiologic factor in its production is complete bronchial obstruction. We shall show in this series that in complete bronchial obstruction, by the normal play of gas exchanges a complete absorption of gases from the alveoli and atelectasis ensue. This concept will be elaborated in the second and third papers of this series, entitled, respectively, "The Behavior and Absorption Times of Oxygen, Carbon Dioxid, Nitrogen, Hydrogen, Helium, Ethylene, Nitrous Oxid, Ethyl Chlorid and Ether in the Lung" and "A Theory of Air Absorption in Atelectasis."

During the course of our studies we developed a technique for following closely under direct vision the gas exchanges within the lungs from the time of complete bronchial obstruction to the completion of atelectasis. The methods to be described have been unusually valuable in giving us an insight into the finer mechanism of the production of atelectasis and the exchange of various gases through the pulmonary endothelium. In addition, they offer an excellent opportunity for further studies on the lung, be it from the standpoint of the thoracic surgeon, the anesthetist, the internist or the physiologist.

We shall describe below the indirect, or "closed-chest" technique, and the direct, or "open-chest" technique. With both methods complete bronchial obstruction is obtained by a special type of cannula through which gas samples may be drawn from below the obstructed portion of the lung. With the first method the pulmonary changes are followed by Roentgen ray and fluoroscopy, the chest being intact. By the second technique the chest is wide open, allowing direct observation of the lungs through an "oscillating negative pressure box" which closely simulates the physiologic condition of a closed thorax. In the second and third papers of this series, to follow, we shall describe the results and theoretical and practical conclusions arrived at with the aid of these methods, described below.

Technique. In previous papers we showed that atelectasis can be constantly produced experimentally if a bronchus is obstructed in

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studies we developed a technique for division the gas exchanges within the bronchial obstruction to the methods to be described have been an insight into the finer mechanism and the exchange of various gases helium. In addition, they offer an studies on the lung, be it from the balloon, the anesthetist, the internist

direct, or "closed-chest" technique, " technique. With both methods is obtained by a special type of ples may be drawn from below the

With the first method the pulmonary Roentgen ray and fluoroscopy, the old technique the chest is wide open, the lungs through an "oscillating" closely simulates the physiologic the second and third papers of this be the results and theoretical and with the aid of these methods,

we showed that atelectasis can be ally if a bronchus is obstructed in

an air-tight manner. For this purpose we elaborated a specially constructed one-way valve elastic balloon, which was introduced by the bronchoscope into a chosen bronchus of the dog. This balloon (Fig. 1), described elsewhere,¹⁰ can be inflated from the outside and then detached from its connection and left in place. Ten to 15 hours later roentgenographic examination of the animal, placed on a special stand for obtaining symmetrical pictures, shows the characteristic pictures of atelectasis with the displacement of the heart, the trachea and the diaphragm to the affected side and opacity of the affected lung. We believe that if we were able to produce atelectasis regularly it was because we used as an obstructive agent an elastic balloon and not a solid plug of cork, wood or

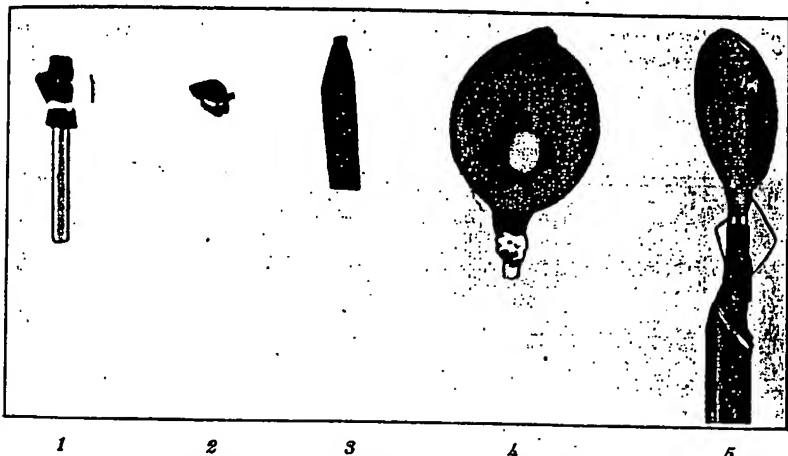


FIG. 1.—The balloon used for the obstruction of a bronchus in an air-tight manner. 1, A glass tube, 4 cm. long and a little less than 0.5 cm. across. Over its distal end a piece of old rubber glove, about 2 by 3 cm., has been placed with a double lateral twist and tied. A one-way valve in the direction of the arrow is thus formed. 2, End or head-on view of the valve, showing the lateral twists of the rubber in the formation of the valve. 3, A piece of rubber Kollman tubing, about 4 cm. long, into which the glass and valve are introduced. 4, The rubber tubing has been tied in an air-tight manner around the glass tube, 1 cm. from its proximal end, "E," and air has been inflated at this end which is open. The balloon is over-inflated to show the perfectly competent valve shimmering through the transparent balloon. 5, The completed balloon, which has an outer protecting cover of organic material, is depicted as having been previously introduced into the desired bronchus in the deflated state. It is now blown and ready to be detached and left in the bronchus. The reader should refer to *Archives of Surgery* (1928, 16, 528) for exact details.

metal, such as that tried by others before and after our investigations. We are convinced that with solid bodies it is almost impossible completely to obstruct a bronchus which yields and the diameter of which changes constantly with expiration and inspiration.

The solution of our present problem, however, required a new technique. We had to devise an instrument that would enable us to obstruct a bronchus completely, through the bronchoscope—in order to avoid opening of the chest or trachea. We must also be

able to draw alveolar air from below the obstruction for determination of gas percentages and intrapulmonary pressure. After a number of trials we constructed two types of apparatus, which gave us full satisfaction.

Intrabronchial Cannulas. The first apparatus is composed of two thin-walled brass tubes of 1 and 2 mm. internal diameter, respectively, and 50 cm. long. The external diameter of both tubes soldered together does not exceed 6 to 7 mm., so that the instrument easily passes through Jackson's full lumen 9-mm. bronchoscope. The narrow tube terminates 15 mm. proximal to the larger one, which is longer and has around its free end a wire crown to avoid obstruction by bronchial mucosa. For the same reason small lateral openings are made around this end. Above and below the distal opening of the small tube two brass rings are soldered around it, each of them bearing a groove for tying the small rubber balloon. Several models with more or less important modifications were made. In Fig. 2 1'-1 shows a bronchial catheter

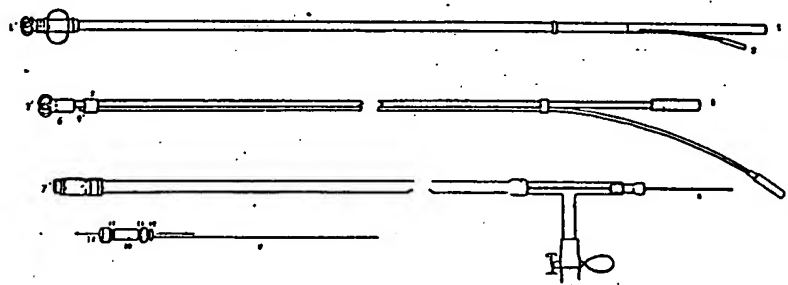


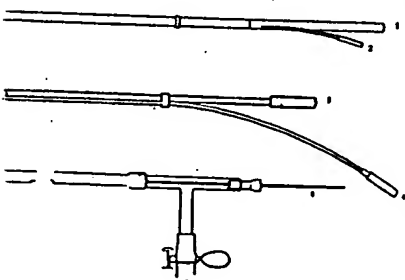
FIG. 2.—Intrabronchial catheters of Coryllos and Birnbaum. Model 1-1' is composed of a large external metal tube (5 mm. in diameter) which terminates in a free end surrounded by a crown (1') in order to avoid closure of this end by bronchial mucosa. A smaller tube passes into this tube and emerges 15 mm. from its distal end (1'), where it is soldered, so that there is no connection between Tubes 1 and 2. Around the distal end of the small tube is tied a piece of Kollman rubber tube, so that when air or fluid is introduced through 2 the rubber is distended, forming an obstructing balloon, as outlined. 3-3' is the model described in the text, showing 3-3', the larger bronchial tube, and 4-4', the smaller one, which serves for the inflation of the obstructing balloon which is not depicted in the diagram. 7-8 is the latest model; it is more detailed but is not essentially different from the preceding ones.

in which the small brass tube passes inside the larger tube throughout its length and emerges near its distal end, where it is filed down level with the outside tube, to which it is carefully soldered. Models 7 and 11 are the latest modification. A piece of fine India rubber tube (the tubing used for Kollman's urethral dilator is excellent) is put over the distal end of the cannula and securely tied around the groove with fine silk thread. This rubber tube is inflated through the small metal tube after the instrument is introduced into the chosen bronchus and forms an obstructing balloon. The

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below the obstruction for determination of intrapulmonary pressure. After a two types of apparatus, which gave

The first apparatus is composed of a tube of 1 and 2 mm. internal diameter, and an external diameter of both tubes not exceed 6 to 7 mm., so that the tube is as large as Jackson's full lumen 9-mm. tube. The tube terminates 15 mm. proximal to the obstruction and has around its free end a wire which is inserted into the bronchial mucosa. For the same purpose, two brass rings are made around this end. Above the small tube two brass rings are made bearing a groove for tying the models with more or less important obstructions. Fig. 2 1'-1 shows a bronchial catheter



Coryllos and Birnbaum. Model 1-1' is a tube (5 mm. in diameter) which terminates in a small tube and emerges 15 mm. from its distal end. There is no connection between Tubes 1 and 2. Tube 1 is tied a piece of Kollman rubber tube, so that the rubber is distended, forming an anastomosis with the model described in the text, showing the smaller one, which serves for the inflation of the balloon. 7-8 is the tube not depicted in the diagram. 7-8 is the tube not essentially different from the preceding

is inserted inside the larger tube through its distal end, where it is filed down so that it is carefully soldered. Models are made on. A piece of fine India rubber (the same as an's urethral dilator is excellent) is tied around the cannula and securely tied around the instrument. This rubber tube is inflated after the instrument is introduced into the chest as an obstructing balloon. The

PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION 321

accurate inflation of the balloon is one of the most important points of the technique. It must be sufficient to obstruct the bronchus completely but not so excessive as to interfere with the circulation or innervation of the bronchus or with the ventilation of the other bronchi by displacement of the interbronchial spur or carina. These requirements are imperative, since, as a rule, these experiments last for many hours. It is necessary to know at all times whether the degree of inflation and obstruction remains unchanged. For this reason we devised a closed mercury manometer system

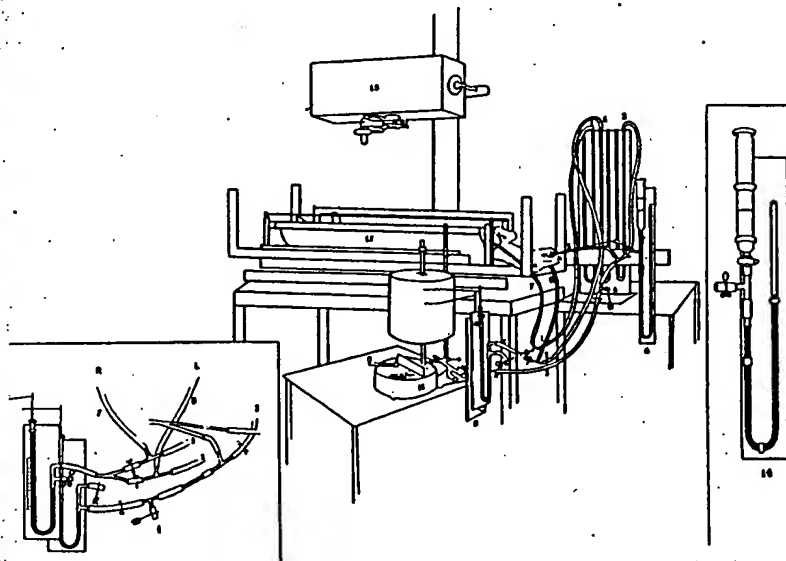


Fig. 3.—Lay-out of closed chest experiment. The animal is placed on our special Roentgen ray stand (12) and the bronchus blocked by means of the intrabronchial catheter (5) connected to the mercury manometer (6) (enclosure 14), which allows checking up its degree of inflation. In each pleural cavity a cannula is placed connected to rubber tubes 7 and 8. These tubes are connected (left enclosure) by T tubes to water manometers (1 and 2) and through another tube to a recording mercury manometer, so that it is possible to record on the smoked drum the tracing of the left or right pleural cavity pressure. The large bronchial tube of the bronchial catheter is connected by a T tube to a water manometer (3) and to a mercury manometer recording on the same smoked-drum (11). A T-tube was interposed in the latter rubber tube (4, left enclosure), allowing the taking of air specimens of intrapulmonary air for gas analysis. 13 is the adjustable fluoroscope or Roentgen ray unit.

(Fig. 3, 14), the free end of which was connected by way of a T tube to a syringe of 30 cc. capacity. The horizontal tube was connected through a rubber tube to the small tube of the bronchial catheter. By pushing down the plunger of the syringe, already filled with water, we could inflate the balloon to a size a little greater than the estimated diameter of the bronchus on which bronchoscopy had previously been done, and a marker was placed at the height of the

mercury meniscus in the closed end of the manometer. The bronchial catheter would then be disconnected. After it was introduced through the bronchoscope into the chosen bronchus it would again be connected with the manometer and the plunger of the syringe pushed in to distend the balloon and bring the mercury meniscus slightly above the previously placed marker. As long as the mercury stood at this level we were certain that the balloon was inflated.

Two types of experiments were carried out.

I. CLOSED-CHEST METHOD. In the first group, which will be designated by "closed-chest method" (Fig. 3), the animal, under iso-amyl-ethyl barbituric anesthesia, was placed on the Roentgen ray stand (12) so that the evolution of the experiment could be watched by fluoroscopy and Roentgen ray pictures. The intrapleural pressures during the experiment were taken by two water manometers (1, 2) connected with two cannulas introduced into the pleural cavities of the animal. Through the bronchoscope the pulmonary cannula was introduced and the balloon inflated, as already described. The larger tube of the bronchial catheter, which communicated with entrapped pulmonary air, was connected to a water manometer (3), to a recording mercury manometer and at times through a T tube (4) to the sampling bulb for analysis of specimens of alveolar air by a modified Henderson-Bailey gas analyzer. In this way it has been possible to follow simultaneously the intrapleural pressures and to record them on a smoked drum (11), to read and record the intrapulmonary pressure in the obstructed lung, to follow the changes in percentage of the entrapped alveolar air and to check up by fluoroscopy and roentgenographic examination the progress of atelectasis. At the same time the closed mercury manometer connected with the small tube of the intrabronchial catheter enabled us to know exactly the degree of inflation of the obstructing balloon.

II. OPEN-CHEST METHOD. The animal was anesthetized with sodium iso-amyl-ethyl barbiturate, 55 mg. per kilogram intraperitoneally. The neck was then shaved, the anterior wall of the chest prepared and intratracheal insufflation through the bronchoscope started. The thorax was then opened by hemisection of the sternum and a Balfour retractor was applied to maintain both thoracic cavities wide open. In the meantime (Fig. 4) a rotating valve (8) was connected with the suction faucet (10) and the number of its revolutions per minute regulated to the respiratory rate of the animal as it was before opening of the chest. The intrapleural pressure was taken before operation and the oscillations of negative pressure in the box (indicated in the water manometer, 9) were regulated so as to be equal to the intrapleural pressure of the animal before opening of the chest. The animal was then transported to the box and its head passed rapidly through the circular

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opening of it. During this short time intratracheal insufflation was discontinued without any evil effect. The cover was tightly applied and the rubber collar fixed around the neck of the animal, smeared with petrolatum and secured by a gauze bandage or by a pneumatic collar, a later modification. Care was taken not to exert any unnecessary constriction around the neck. From now on the intratracheal insufflation can stop and the animal will

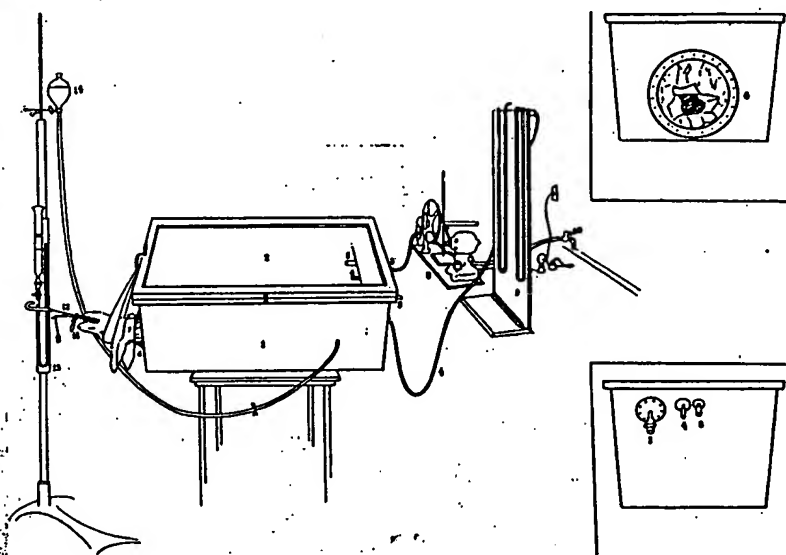


FIG. 4.—Lay-out of the open chest experiment in the oscillating vacuum box. After the chest is opened the animal is placed in the air-tight box (1), the cover of which (2) is made of plate glass. The head of the animal protrudes through the opening in the box (upper right corner enclosure 6, and also Fig. 6), around which is fixed an inflatable rubber collar which fits snugly around the shaved and petrolatum-anointed neck of the animal. The rotating valve (8), interspersed between the suction apparatus (10) and the box inlet (3), insures an oscillating vacuum in the box. This pressure is measured by the water manometer (9) and is equal to the negative intrapleural pressure of the animal taken previous to the operation. Inlet 5 serves to regulate the pressure in the box. A rubber tube passes through one wall of the box and may be connected to a reservoir with physiologic solution of sodium chloride; by this means fluids can be administered under the skin or into the peritoneum of the animal during the experiment. Through the bronchoscope (11) the bronchial cannula is introduced into the left stem bronchus, and the balloon which is to occlude the bronchus is then inflated by means of the syringe-mercury manometer arrangement described in Fig. 3. The large tube of the cannula, in communication with the entrapped intrapulmonary air, is closed off unless samples of air are to be withdrawn through it for gas analysis.

breathe with its chest wide open at the same rate and with the lungs under the same negative pressure as in the closed-chest. Moisture and temperature inside of the box were kept as near normal as possible. Fig. 5 is a photograph of the layout of the whole experiment. It has been repeatedly possible to keep the animal in fine condition in the box for from 8 to 15 hours. A small tube was

provided for, through which saline solution, cardiotonics, or additional anesthetics could be given subcutaneously, if necessary, without disturbing the experiment. The pulmonary cannula was then introduced as for the "closed-chest" method.

We wish to point out that this box is based on a different principle from the differential pressure chamber of Sauerbruch. In the latter, only one pleural cavity being open, the steady and non-oscillating differential pressure (hypo or hyper) serves to keep the lung of the opened half-chest distended while the other lung breathes normally. In our box (Fig. 5), on the contrary, both pleural cavities being widely opened, no respiration can take place unless

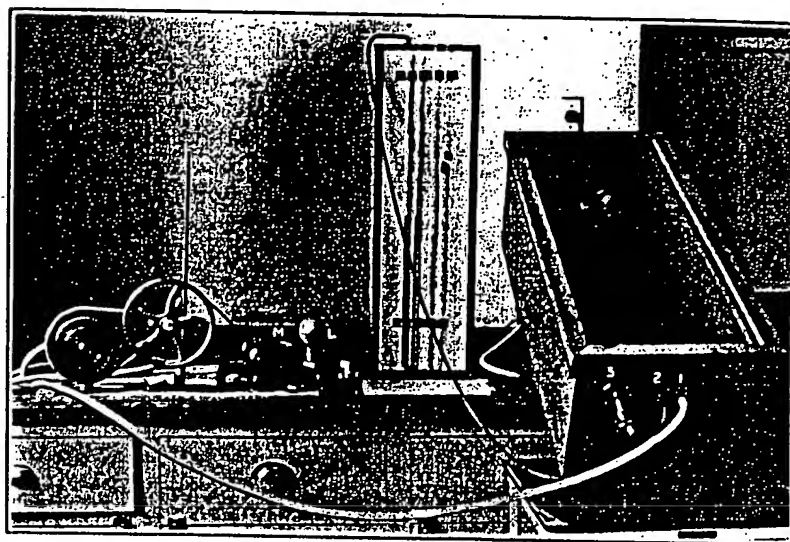
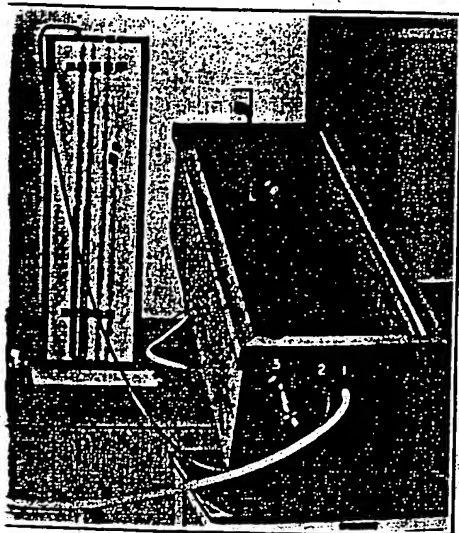


FIG. 5.—Box for oscillating vacuum. 1, 2 and 3 are outlets corresponding to 3, 4 and 5 of Fig. 4. V, rotating valve; W, speed-reducing wheel; L, 40-watt lamp resistance and C the cylindric collar, for the neck of the animal, which has lately been replaced by the inflatable rubber collar shown in Fig. 6.

there is an oscillation in the negative pressure box. It is in an air-tight wooden structure, measuring 33 inches (83.17 cm.) in length, 14 inches (35.48 cm.) in width and 12 inches (30.48 cm.) in height; it is covered by a glass top which runs in a groove in the frame and thus permits the box to be closed hermetically. The groove is filled with mercury or, more conveniently, with petrolatum, so that a perfect seal is obtained. The box has three outlets; two of them are 1.3 cm. in diameter and the third, 0.3 cm. The first outlet is connected with the rotating valve (V) which produces an oscillating vacuum. The valve is rotated slowly by a two-pulley speed-reducing mechanism, consisting of a wheel (W) and a motor (M) with a rheostat installed. An extra 40-watt lamp resistance (L) in the system further reduces the speed of rotation.

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The valve can be regulated to perform the necessary number of
revolutions a minute to make the vacuum interruptions equal to
the respiratory rate before the chest was opened. The rotating
valve is connected at one end with an ordinary suction apparatus
or the laboratory suction faucet. The other end of the rotating
valve connects directly with the box (outlet 1). The second tube
(2) is connected with a water manometer. The third tube (3),
covered with a piece of rubber tubing and stopcock, connects the
box with the outside air, regulating the degree of vacuum in it and
allows the introduction of a thermometer. At the opposite panel
of the box is a circular opening bearing a cylindrical collar (C) of

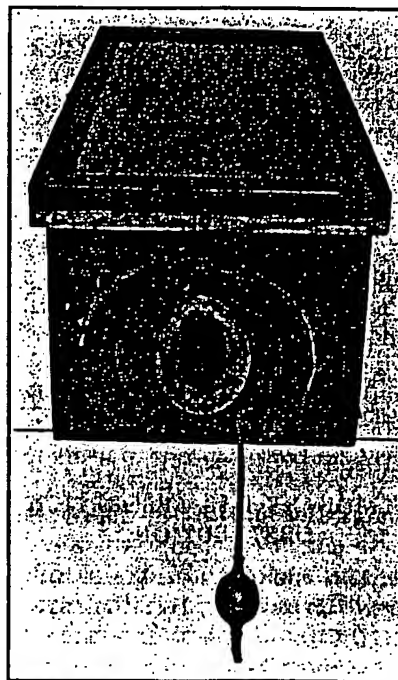


Fig. 6. The inflatable rubber collar of the vacuum box, which fits in an air-
tight manner around the previously shaved and petrolatum-anointed neck of the
animal.

soft rubber tissue which can be adjusted around the shaved neck
of the dog and fixed with a bandage so as to be air-tight. (More
recently we have replaced this collar by a rubber collar which can
be inflated with air.) (Fig. 6.)

By the methods described we have studied the absorption rates
of different gases by the lung. These are described in a paper to
follow. Using this technique it soon occurred to us that after the
bronchial catheter was in place and a lobe of lung occluded, atelec-
tasis could be expedited by mechanically withdrawing all the air
or gas from it with a syringe and then washing out the lobe by

successively (6 or 7 times) introducing and withdrawing several hundred cubic centimeters of fresh oxygen each time, the lobe finally being left collapsed. Now the bronchial cannula is clamped off and the remnants of gases left to absorb until atelectasis occurs—a question of only minutes. "Washing out" with carbon dioxide gives an even more rapid atelectasis. The lobe is now ready for the introduction of the desired volume of gas or gases.

Summary. Two new methods are described which allow a physiologic study of the gas exchanges in a lobe or a whole lung after its bronchus has been completely obstructed.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

II. THE BEHAVIOR AND ABSORPTION TIMES OF OXYGEN, CARBON DIOXID, NITROGEN, HYDROGEN, HELIUM, ETHYLENE, NITROUS OXID, ETHYL CHLORID, AND ETHER IN THE LUNG.

WITH SOME OBSERVATIONS ON PLEURAL ABSORPTION OF GASES.

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AND

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(From the Department of Surgical Research, Cornell University Medical College.)

The phenomena of gas exchanges through a moist and living membrane such as the alveolar endothelium of the lung are quite

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different from those attendant upon simple physical diffusion of a
gas through a porous cup. There is physical and physiologic evi-
dence that they are dependent not only upon the speed of diffusion
of a particular gas through space and its partial pressures or con-
centration on opposite sides of the wet semipermeable membrane
but also upon its solubility and futhermore, in the lung, upon the
integrity of the endothelium and of the intrapulmonary circulation.
The alveolar air is separated from the venous blood by the endothe-
lium of the air sacs and of the capillary vessels which cover their
external surface and by a negligible amount of smooth and of
extremely thin elastic fibers in the walls of the alveolus. Through
this respiratory membrane the exchange of gases takes place.

Solubility of Gases in Fluids. When we regard the lung endothe-
lium as a moist membrane we must consider gas exchanges as
related to their solubility in it. This does not mean that the
endothelium may be regarded as merely a layer of fluid, but the solu-
bility coefficient of different gases in water gives some comparative
basis upon which to formulate absorption times. Moreover, solu-
bility of a gas is dependent upon the nature of the gas, those which
are more basic or acid being more soluble than the neutral ones.*
For example, carbon dioxid is much more soluble than hydrogen.
The volumes of hydrogen, oxygen, carbon dioxid and nitrogen
soluble in 1 cc. of water at body temperature are: Hydrogen, 0.016;
oxygen, 0.024; carbon dioxid, 0.592; nitrogen, 0.016. In a mixture
of gases the amount of each individual gas dissolved in a fluid is
proportional to its partial pressure (Dalton's law). When a defi-
nite volume of liquid is saturated with a gas at constant temperature
and pressure, an equilibrium is established between the gas in solu-
tion and that over the solution.

**Diffusion of Gases Within the Alveoli and Through the Pulmonary
Endothelium.** With a mixture of gases in the alveoli the molecules
of a particular gas diffuse through the alveolar space in all directions
toward the alveolar endothelium at a rate inversely proportional
to the square root of the density of the gas. The velocity
of gas molecules is very great. For example, when hydrogen
and oxygen are in a mixture the hydrogen molecule travels 1840
meters per second and the oxygen molecule travels 460 meters
per second, for the oxygen molecule is 16 times as heavy as
hydrogen ($\frac{1}{\text{square root of } 16} = \frac{1}{4}$). Alveolar air contains approxi-

mately 15 per cent oxygen and 80 per cent nitrogen under atmospheric
pressure; thus 100 cc. of alveolar air would contain 15 cc. of oxygen
and 80 cc. of nitrogen the mixture being under a pressure of one
atmosphere. Since equal volumes of gases under the same pressures
contain equal numbers of molecules, there are 80/15 as many nitrogen

* For the physicochemical aspect of the question see Getman's *Outlines of Theo-
retical Chemistry*, 4th ed., New York, John Wiley & Sons, 1928.

molecules as oxygen molecules in the alveolar air. It is evident therefore, that if nitrogen and oxygen were of equal density, diffusibility and solubility in the alveolar endothelium and peri-alveolar blood, the number of molecules of nitrogen absorbed would be 80/15 as great as for oxygen. Actually we know this is not so, even though the density of nitrogen is almost equal to that of oxygen, oxygen diffusing into the blood much more rapidly than nitrogen which is only soluble to the extent of about 1 per cent in the blood. This is due to the fact that the velocity of diffusion through a moist membrane is not only inversely proportional to the square root of its density, as we have previously said, but also that it is proportional to the coefficient of solubility of the gas in the fluid concerned. That is why the speed of diffusion of carbon dioxide through a wet membrane is 30 times greater than for oxygen, although its density is greater. This can be easily shown by tying shut a frog's lung filled with oxygen or atmospheric air and placing it in an atmosphere of carbon dioxide (Loewy and Luntz). Very rapidly the lung is distended, owing to the diffusion of carbon dioxide into it, for the coefficient of solubility of carbon dioxide is 30 times greater than that of oxygen.

Oxygen and carbon dioxide are not merely dissolved in the plasma of the blood. The bulk of oxygen and carbon dioxide is in chemical combination in the blood. The first combines with hemoglobin, the second with alkali.

The Dissociation Curve of Hemoglobin in Relation to Respiration. The oxygen-hemoglobin compound has the property of dissociating with a fall in the partial pressure of oxygen; this dissociation is complete when the oxygen pressure is reduced to zero. In this way oxyhemoglobin represents an oxygen reserve in the red cells which maintains constant the amount of oxygen dissolved in the plasma, the latter representing the vapor tension of oxygen above the unstable oxygen hemoglobin compound.

Besides the partial pressure of oxygen in the alveolar air or tissues, another important factor in the dissociation of oxyhemoglobin is carbon dioxide. Increase in carbon dioxide hastens the dissociation of oxygen; it "shifts the dissociation curve of oxyhemoglobin to the right" and thus facilitates the unloading of oxygen into the tissues as the carbon dioxide in the blood increases. Although this is strictly correct, it is, according to Haldane,² of much less importance than the shifting of the carbon dioxide absorption curve in consequence of the reduction of hemoglobin.

In fact, decrease of oxygen in the blood and hemoglobin unsaturation increase the capacity of the blood for carbon dioxide, probably because reduced hemoglobin is a more alkaline substance than oxygen-saturated hemoglobin. The latter acting as a weak acid keeps carbon dioxide out of combination with alkali. Whatever the cause of this action may be, it is certain that saturation of hemoglobin decreases the capacity of blood for carbon dioxide, the result being that with high oxygenation the partial pressure of car-

molecules in the alveolar air. It is evident that if nitrogen and oxygen were of equal density, diffusion through the alveolar endothelium and peri-alveolar capillaries would be 80/15. Actually we know this is not so, even though the diffusion coefficient for oxygen is almost equal to that of nitrogen, oxygen diffuses much more rapidly than nitrogen which is at about 1 per cent in the blood. This is due to the greater velocity of diffusion through a moist membrane which is proportional to the square root of its density, as Fick has said, but also that it is proportional to the solubility of the gas in the fluid concerned. That is why the rate of diffusion of carbon dioxide through a wet membrane is much greater than for oxygen, although its density is greater. This is shown by tying shut a frog's lung filled with air and placing it in an atmosphere of carbon dioxide (Krogh and Lantieri). Very rapidly the lung is distended, and carbon dioxide enters it, for the coefficient of diffusion for carbon dioxide is 30 times greater than that of oxygen. Carbon dioxide is not merely dissolved in the plasma of the blood but is in chemical combination with hemoglobin.

of Hemoglobin in Relation to Respiration. Hemoglobin compound has the property of dissociation in the presence of partial pressure of oxygen; this dissociation is reversible. When the oxygen pressure is reduced to zero. It represents an oxygen reserve in the red cells. The amount of oxygen dissolved in the blood is small compared with the amount of oxygen above the vapor tension of oxygen above hemoglobin compound.

When the partial pressure of oxygen in the alveolar air or tissues, falls, the dissociation of oxyhemoglobin is hastened. The dissociation curve of oxyhemoglobin states the unloading of oxygen into the blood as the partial pressure of oxygen in the blood increases. Although this is true, the amount of oxygen dissolved in the blood is much less important than the carbon dioxide absorption curve in the blood and hemoglobin unsaturation.

Carbon dioxide in the blood and hemoglobin unsaturation is a more alkaline substance than oxygen. The latter acting as a weak acid in combination with alkali. Whatever may be, it is certain that saturation of the blood for carbon dioxide, the oxygenation the partial pressure of car-

bon dioxide in the blood rises although its percentage remains the same. For this reason more carbon dioxide is given off by the blood when its oxygen saturation is high (Werigo,³ Bohr, Hasselbach and Krogh⁴). Now it follows that if one lung is ventilated with a neutral gas as hydrogen, and the other with air, the latter will give off nearly 50 per cent more carbon dioxide than the former. (Haldane.)

A decrease in carbon dioxide has another important result, discovered by Bohr⁵ (1904) and called the "Bohr effect." Such a decrease shifts the dissociation curve of hemoglobin to the left so that whereas in the venous blood (carbon dioxide, 45 mm. of mercury; oxygen, 40 mm. of mercury) the hemoglobin is 68 per cent saturated, if carbon dioxide falls to 10 mm. of mercury the hemoglobin (without any increase in the oxygen pressure) becomes 85 per cent saturated. Furthermore, the oxygen is more firmly held in combination with hemoglobin so that notwithstanding this apparent increase in oxygen pressure and absence of cyanosis, the oxygen available to the tissues is greatly diminished.

Oxygen and carbon dioxide in the alveoli are kept quite constant at about 15 and 5 per cent, in spite of a constant interplay of gases through the alveolar endothelium. The inspiratory draft of air carries oxygen down only to a certain level in the bronchial tree; from this level oxygen, at a higher partial pressure, diffuses down through the larger and smaller bronchi and finally into the alveolar sacs where oxygen is at a lower partial pressure due to its continuous absorption from the alveoli into the blood. Similarly, on expiration, carbon dioxide is carried out of the alveoli only into the medium size bronchi, and from there it diffuses toward the larger bronchi and trachea. The mechanical carriage of oxygen and carbon dioxide in and out of the lung in the respiratory air drafts is thus a limited process, which depends upon the diffusibility of these gases to carry oxygen into the alveoli and tissues, and carbon dioxide out of the tissues and alveoli into the external air. This is, briefly, part of the intricate mechanism which, as previously stated, regulates the percentages of alveolar oxygen and carbon dioxide with such nicety.

With a lobe containing air or other of the gases studied, cut off from the outside air by complete bronchial occlusion, the same factors we have considered in previous paragraphs come into play to bring about a complete absorption of alveolar gases (and atelectasis). The exact mechanism we leave to a succeeding paper.⁶ In this paper we shall give some typical protocols, comment on the phenomena of gas exchanges when one or more gases are introduced into an occluded lobe, and summarize, as far as the present studies allow, the actual absorption times of a stated amount of gas by one lobe of the lung. For the exact technique the reader should refer to a previous paper.⁷

Changes in Entrapped Alveolar Air as Indicated by Successive Gas Analyses. The results obtained in closed as well as open chest experiments show that within 2 to 7 minutes after bronchial obstruc-

tion the oxygen percentage falls rapidly from 15 to 5 or 6 per cent. It remains at about these figures until complete disappearance of the alveolar air. (Table 1.)

TABLE 1.—CHANGES IN OXYGEN AND CARBON DIOXID PERCENTAGES AFTER OBSTRUCTION.*

Dog.	Time after obstruction.	Oxygen.	Carbon dioxide.	Comment.
466 . .	Before bronchial obstruction	14.20	4.80	
	5 min.		4.09	
	35 min.	2.09	4.12	
	2 hrs. 50 min.	4.00	5.30	Animal dyspneic and cyanotic.
	2 hrs. 20 min.	5.70	6.07	Animal breathes quietly.
475 . .	10 min.	3.90	6.40	
	25 min.	3.90	4.70	
	50 min.	16.70	3.09	Obstructing balloon broke.
482 . .	10 min.	6.10	6.20	
	25 min.	6.04	6.26	
	40 min.	6.57	6.49	
	55 min.	5.41	6.71	
	5 hrs. 15 min.	6.81	6.45	
	6 hrs. 15 min.	5.35	6.97	
	10 hrs. 15 min.	5.81	5.53	

* Only figures in which possibility of error in gas analysis was excluded are given in this table.

In animals in which gas analyses were performed until complete atelectasis occurred, the curves plotted for percentages of oxygen and carbon dioxide show that the percentages vary inversely. (Fig. 1.) It is thus seen that the entrapped alveolar air rapidly undergoes marked quantitative changes, the percentage of oxygen dropping and carbon dioxide rising so that their respective partial pressures tend to come into equilibrium with the corresponding gases of the venous blood. These changes occur in exactly the same way in animals as in man, as shown by Loewy and von Schroetter³ (1905).

The succession of events as observed in the open-chest experiment, with the lung normally breathing in air, is as follows: Immediately after successful obstruction "the lung stops breathing," whereas the normal lung increases in size. There is a slight inspiratory excursion in the occluded lung owing to the decrease of pressure (increased negative pressure) in the box during inspiration, but it is insignificant as compared to the wide respiratory movements of the other lung. Little by little the size of the occluded lung decreases as a whole, without a conspicuous change in its general shape, appearance or color. Gradually it sinks toward the costovertebral sinus, whereas the other lung increases in size so that the heart is manifestly displaced toward the obstructed lung. Except for a slight cyanotic hue, the obstructed lung does not show any other

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GEN AND CARBON DIOXID PERCENTAGES AFTER OBSTRUCTION.*

Oxygen.	Carbon dioxide.	Comment.
14.20	4.80	
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3.90	4.70	
16.70	3.09	Obstructing balloon broke.
6.10	6.20	
6.04	6.26	
6.57	6.49	
5.41	6.71	
6.81	6.45	
5.35	6.97	
5.81	5.53	

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PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION 331

change until its volume is markedly decreased (to about one-fifth or one-seventh its original size). Then there appear dark bluish-brown patches scattered all over its surface without any predilection for the hilus or peripheral portion of the lung, as van Allen and Adams⁹ reported. After the great mass of gas is absorbed atelectasis advances rapidly, and within approximately 1 hour is complete. Figs. 2 and 3 show histologic sections of atelectasis produced in open- and closed-chest experiments. Often small islands of slightly aerated light-colored parenchyma remain on the dark bluish-black atelectatic lung, the complete disappearance of which may take half an hour or more. This general picture was

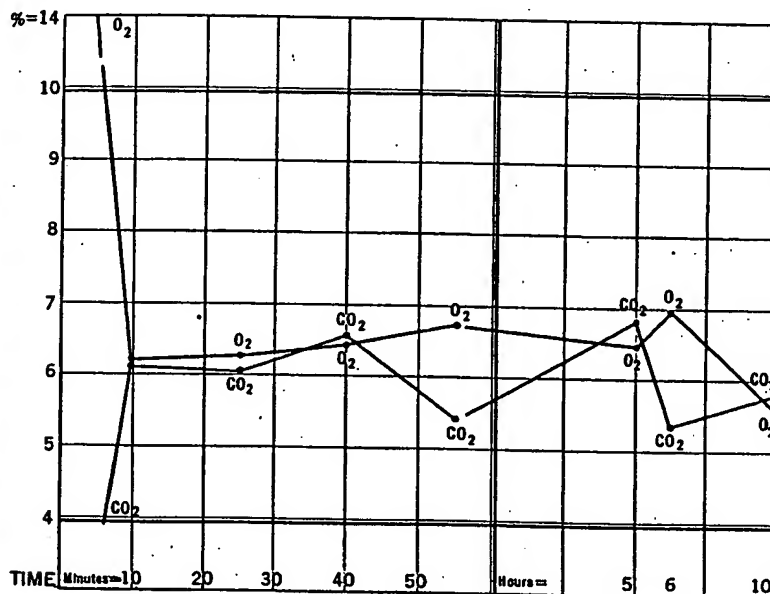


FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction. Dog. 482, March 30, 1930.

observed, as well, with gases other than air; only the time factor varied.

The actual volumes of gases introduced for the study of their absorption varied from 100 to 500 cc. of gas, depending for the most part upon the size of the animal. In the case of ether the pure vapor was obtained by slowly passing liquid ether through a metal coil immersed in water at 90° C., the coil in turn being directly connected to the lobe of lung under study through the pulmonary cannula. Ethyl chlorid was introduced directly in a spray from a standard commercial container through a long tube so that it reached the lung as a vapor. For the latter two vapors the volume

introduced was judged by the state of inflation of the lobe as compared to the inflation produced by measured volumes of gases previously introduced. The other gases were measured, as injected, with a P. A. Stoss-Nachfolger pneumothorax apparatus. The absorption times of a gas refer to the approximate period for absorption of gas in a lobe inflated to its full inspiratory state (for a given animal, to the same degree for each gas). It should be noted that the volumes of gas and their "absorption times" are given and not the "absorption rate." The actual "absorption rates" would have to be given in terms of cubic centimeters of gas per minute per square centimeter of absorbing surface of the lung at the particular time; this would be very difficult because the circulation and the area of the absorbing surface of a lobe are variable factors depending upon the particular state of inflation of the lung at any one moment. There are two opposing factors which normally regulate absorption. As the lung shrinks down the alveolar capillary circulation becomes progressively poorer as we have shown elsewhere,¹⁰ but the relative absorbing surface becomes greater per unit volume of contained gas, since the volume of an alveolus decreases relatively much more than its surface. (Fig. 4.)

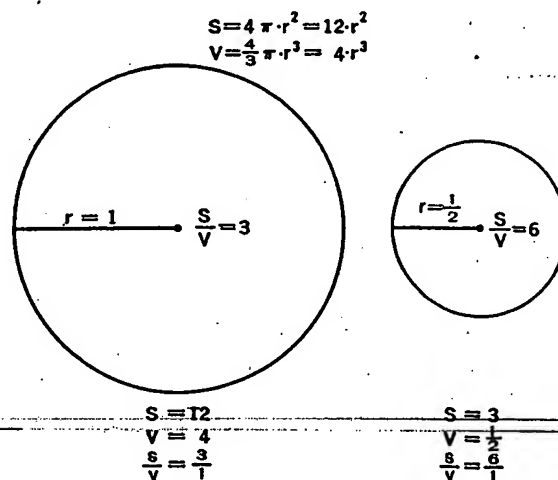


FIG. 4.—Showing the mathematic acceleration in absorption rate of gases in the alveoli of the lung. These relations probably hold true up to a point where the capillary circulation is definitely impaired.

Absorption of Oxygen and Carbon Dioxid. Closed-chest experiment. Dog 489. The experiment lasted 9½ hours.

May 5, 1930. 11.45 p.m.: The rubber balloon on the cannula was introduced into the right lower bronchus.

11.52 p.m.: The balloon was blown up with 3 cc. of water.

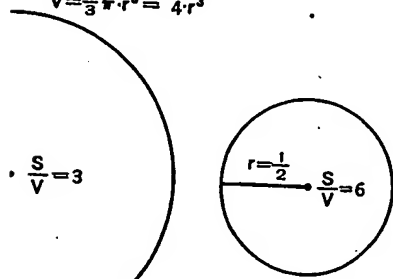
11.54 p.m.: A sample of gas was obtained from the obstructed lung, 15 cc.; it contained 5.85 per cent carbon dioxid and 9.05 per cent oxygen.

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by the state of inflation of the lobe as compared by measured volumes of gases produced. The other gases were measured, as injected, Nachfolger pneumothorax apparatus. The as refer to the approximate period for absorbed to its full inspiratory state (for a given degree for each gas). It should be noted as and their "absorption times" are given ion rate." The actual "absorption rates" n in terms of cubic centimeters of gas per timeter of absorbing surface of the lung at is would be very difficult because the circ- the absorbing surface of a lobe are variable the particular state of inflation of the lung There are two opposing factors which nor- on. As the lung shrinks down the alveolar omes progressively poorer as we have shown tive absorbing surface becomes greater per ned gas, since the volume of an alveolus h more than its surface. (Fig. 4.)

$$S = 4\pi \cdot r^2 = 12\pi r^2$$

$$V = \frac{4}{3}\pi \cdot r^3 = 4\pi r^3$$



$\frac{12}{4}$	$\frac{S}{V} = 3$
$\frac{3}{1}$	$\frac{S}{V} = \frac{6}{1}$

natic acceleration in absorption rate of gases in the ations probably hold true up to a point where the r impaired.

id Carbon Dioxid. Closed-chest experiment. asted 9 1/2 hours.

∴ The rubber balloon on the cannula was er bronchus.

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FIG. 2.—Photomicrograph showing atelectasis produced in the open-chest experiment.

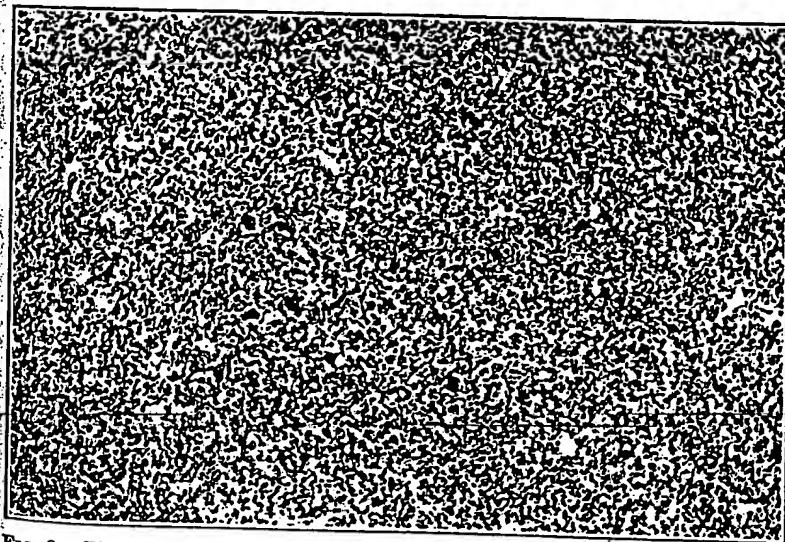


FIG. 3.—Photomicrograph showing atelectasis produced in the closed-chest experiment.

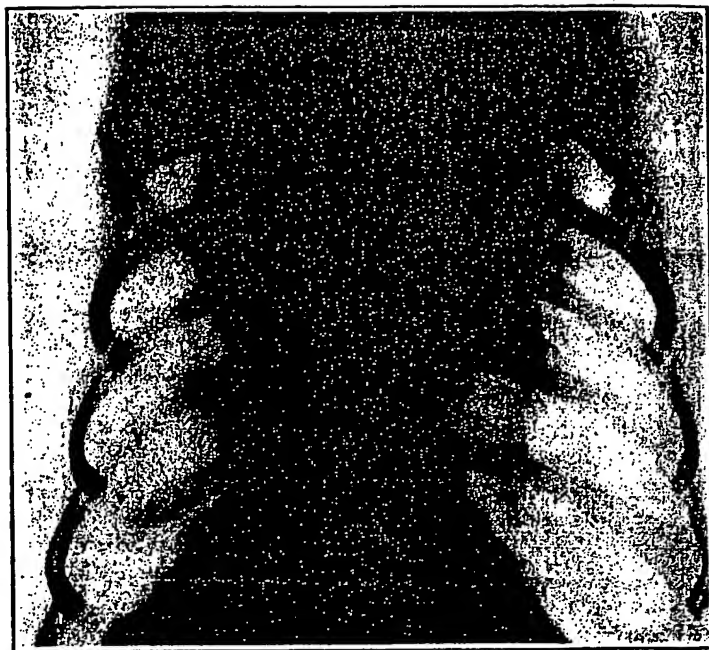


FIG. 5A

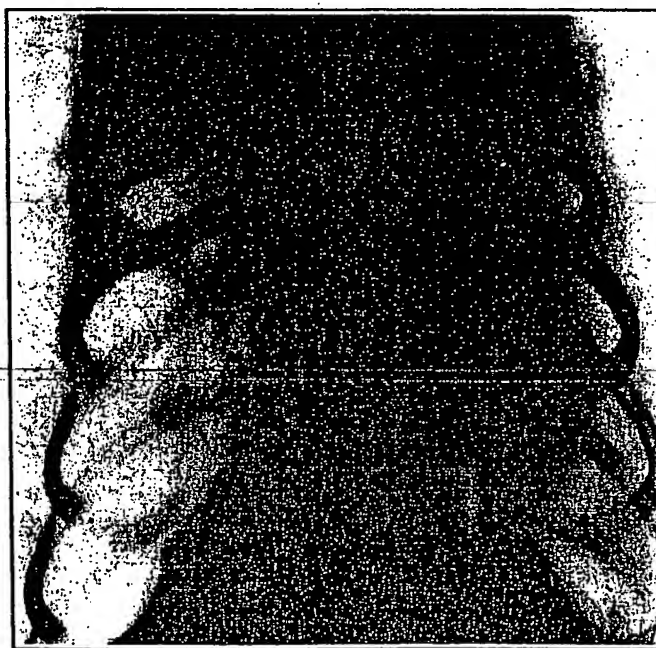


FIG. 5B

FIG 5.—Dog 511. *A* was taken after the introduction of 290 cc. CO₂ into the left lower lobe which appears distended. *B* was taken 10 minutes after the introduction of CO₂ into the left lower lobe. The gas has been completely absorbed.



FIG. 5A

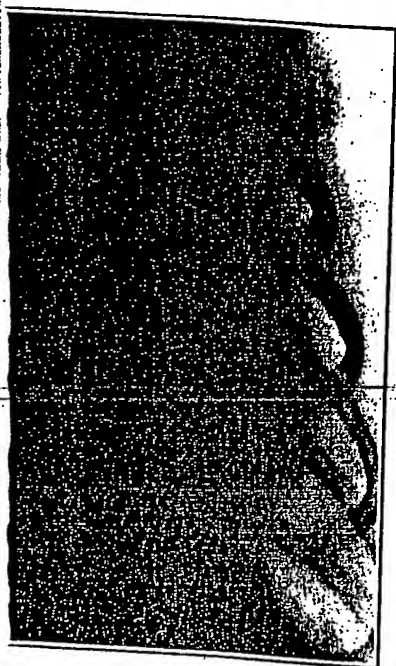


FIG. 5B

after the introduction of 290 cc. CO₂ into the pleural space. B was taken 10 minutes after the introduction. The gas has been completely absorbed.

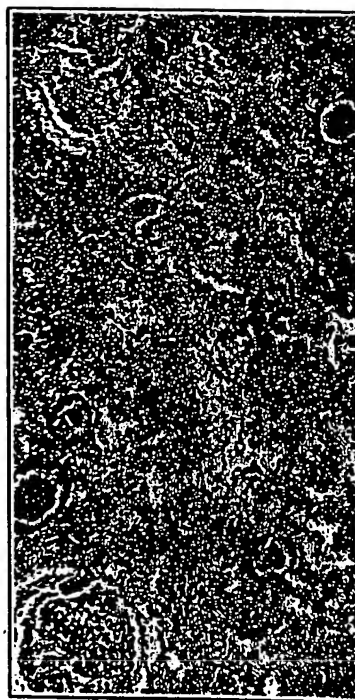


FIG. 6.—Interstitial hemorrhage and edema in the left lower lobe after introduction of 100 per cent ether vapor into the lung previously rendered atelectatic (open chest experiment).



FIG. 7A

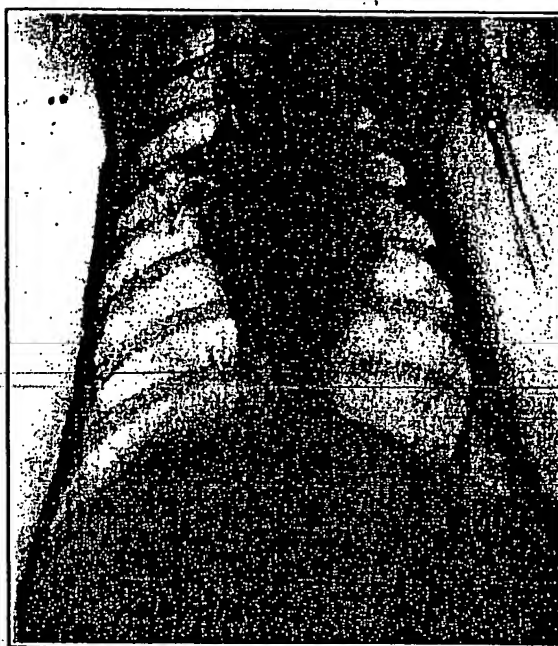


FIG. 7B

FIG. 7.—A, roentgenogram of a rabbit's chest after introduction of 75 cc. oxygen into the right pleural cavity. B, after complete absorption of gas from the pleura cavity; the heart has returned to its normal position.

2.03 A.M.: A sample of gas contained 5.98 per cent carbon dioxide and 51.2 per cent oxygen.

2.17 A.M.: A sample of gas contained 5.9 per cent carbon dioxide and 51.2 per cent oxygen.

2.28 A.M.: A sample of gas contained 6.1 per cent carbon dioxide and 51.2 per cent oxygen.

2.41 A.M.: A sample of gas contained 6.07 per cent carbon dioxide and 51.2 per cent oxygen.

2.52 A.M.: A sample of gas contained 6.05 per cent carbon dioxide and 51.2 per cent oxygen.

3.21 A.M.: Only 2 cc. of gas could be obtained.

3.35 A.M.: A roentgenogram showed a definite shift of the heart to the left.

3.53 A.M.: 100 cc. of oxygen was introduced into the obstructed lung. Roentgenograms taken 1 and 2 minutes later showed the heart shifted to the left.

4.58 A.M.: A sample of gas from the obstructed lung contained 6.94 per cent carbon dioxide and 51.2 per cent oxygen.

5.10 A.M.: A roentgenogram showed the heart again back to the right.

5.15 A.M.: Only 4 cc. of gas could be obtained; this amount was insufficient for analysis.

5.22 A.M.: Fluoroscopy showed the heart a little more to the right than before the administration of oxygen. The respiration was very quiet.

5.40 A.M.: Fluoroscopy showed increased density of the right lower lung.

5.46 A.M.: 100 cc. of carbon dioxide was introduced into the obstructed lung.

5.49 A.M.: The heart was shifted to the left; the right lower lobe was inflated.

5.50 A.M.: Only 4.8 cc. of gas could be obtained. It contained 54.16 per cent carbon dioxide.

5.52 A.M.: A roentgenogram showed the heart back again on the right; breathing was very quiet.

5.55 A.M.: Fluoroscopy showed no further change; the right side of the diaphragm was immobile, and the heart moved toward the right on inspiration. There was no ventilation in the obstructed lung.

5.56 A.M.: A roentgenogram showed no change. The animal was anesthetized with 30 cc. saturated solution of magnesium sulphate injected intravenously.

6.02 A.M.: Autopsy revealed atelectasis of the right lower and accessory lobes (confirmed by microscopic sections). (See Figs. 5A and 5B, Plate I.)

Experiment. Dog. 498, 10 kg. The experiment lasted 14 hours. Negative pressure was -4, -7.5 of water; oscillation rate, 14 per minute. Temperature in the box, 40° C.

May 15, 1930. 11.35 A.M.: The left lung was obstructed.

11.40 A.M.: A sample of gas contained 6.09 per cent carbon dioxide and 51.2 per cent oxygen.

11.45 A.M.: Atelectasis was complete in 9 hours.*

11.50 A.M.: 100 cc. of oxygen was introduced to distend the left lower lung.

11.55 A.M.: A sample of gas contained 8.59 per cent carbon dioxide; the percentage was beyond the limit of the apparatus.

In these experiments we were able to know with certainty when atelectasis was complete by the characteristic dark bluish color of the lung; this was repeatedly verified by histologic sections.

- 11.00 P.M.: The left lower lobe was again atelectatic; all the gas was absorbed.
- 11.10 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.
- 11.20 P.M.: The left lower lobe was again atelectatic; all gas was absorbed.
- 11.25 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.
- 11.31 P.M.: The left lower lobe was much smaller; 100 cc. more of oxygen was introduced.
- 11.35 P.M.: A sample of gas contained 10.63 per cent carbon dioxide; the oxygen percentage was beyond the limit of the apparatus.
- 12.13 A.M.: 100 cc. of carbon dioxide was introduced to distend the left lower lobe.
- 12.14½ A.M.: All the carbon dioxide was absorbed; the lobe was again atelectatic.
- 12.16 A.M.: 100 cc. of oxygen was introduced to distend the left lower lobe again.
- 12.27 A.M.: The oxygen was completely absorbed; the lower left lobe was again atelectatic.
- 12.37 A.M.: 50 cc. of oxygen and 50 cc. of carbon dioxide was introduced to distend the lower left lobe.
- 12.41 A.M.: All the gas was absorbed; the lobe was again atelectatic.
- 1.02 A.M.: 150 cc. of 100 per cent ether vapor was introduced to distend the lower lobe.
- 1.03 A.M.: All the ether was absorbed; the lobe was atelectatic again.
- 1.09 A.M.: 100 cc. of nitrogen was introduced into the left lower lobe.
- 1.25 A.M.: The heart stopped beating; the lung was unchanged.
- Summary.* The absorption time for oxygen in this experiment averaged 15 minutes; for carbon dioxide, 1.5 minutes; for 100 per cent ether vapor, 1 minute.

TABLE 2.—ABSORPTION TIMES OF OXYGEN AND CARBON DIOXIDE INDIVIDUALLY INTRODUCED IN A LUNG PREVIOUSLY RENDERED ATELECTATIC.

Dog.	Oxygen.		Carbon dioxide.		Comment.
	Cc.	Absorption time, min.	Cc.	Absorption time, min.	
511	150	15	290	5	Closed chest experiment; roentgenographic control; other gases besides oxygen and carbon dioxide were successively introduced.
	275	15	275	5	
	280	12	250	7	
507	100	2½	Open-chest experiment.
504	100	2	Open-chest experiment.
498	100	10 and 11	100	1½	Open-chest experiment.
499	275	13	300	3	Open-chest experiment.

The figures in Table 2 show that the absorption times of oxygen and carbon dioxide show a constancy which is in agreement with the physical laws of diffusion and solubility. These times, however, seem to vary according to the anatomic conditions of the alveolar endothelium. This supposition is made on the basis of findings in Dog 504, in the atelectatic lungs of which were successively intro-

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lobe was again atelectatic; all the gas was
 gen was introduced to distend the left lower
 lobe was again atelectatic; all gas was ab-
 gen was introduced to distend the left lower
 lobe was much smaller; 100 cc. more of
 as contained 10.63 per cent carbon dioxid;
 yond the limit of the apparatus.
 on dioxid was introduced to distend the left
 n dioxid was absorbed; the lobe was again
 gen was introduced to distend the left lower
 as completely absorbed; the lower left lobe
 n and 50 cc. of carbon dioxid was introduced
 s absorbed; the lobe was again atelectatic.
 per cent ether vapor was introduced to dis-
 as absorbed; the lobe was atelectatic again.
 gen was introduced into the left lower lobe.
 ped beating; the lung was unchanged.
 time for oxygen in this experiment averaged
 , 1.5 minutes; for 100 per cent ether vapor,

OF OXYGEN AND CARBON DIOXID INDIVIDUALLY
 PREVIOUSLY RENDERED ATELECTATIC.

Carbon dioxid.		Comment.
	Absorption time, min.	
0	5	Closed chest experiment; roent- genographic control; other gases besides oxygen and carbon dioxid were successively introduced.
5	5	
0	7	
0	2½	Open-chest experiment.
0	2	Open-chest experiment.
0	1½	Open-chest experiment.
0	3	Open-chest experiment.

now that the absorption times of oxygen
 constancy which is in agreement with the
 and solubility. These times, however,
 the anatomic conditions of the alveolar
 tion is made on the bases of findings in
 lungs of which were successively intro-

PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION 335

duced in the following order: nitrous oxid, carbon dioxid, ethyl
 chlorid, ethylene, carbon dioxid, ethyl chlorid, carbon dioxid,
 ethylene, oxygen and ether vapor. Because of the lesions of pul-
 monary endothelium by the gases introduced in it, carbon dioxid
 at the first introduction was absorbed in 2 minutes; at the second
 introduction, in 21 minutes, and at the third introduction, in 1 hour
 and 22 minutes.

Nitrogen when introduced alone under atmospheric pressure into
 the atelectatic lung was absorbed within 16 hours in Dog. 517.
 When pure nitrogen or other neutral gases, as hydrogen or helium,
 are introduced into an atelectatic lung, gas analysis of the alveolar
 content shortly thereafter shows that oxygen and carbon dioxid are
 present in the same percentage as in the alveolar blood, that is,
 about 5 or 6 per cent each. At the same time under fluoroscopic
 examination we found that after introduction of nitrogen there is
 at first a slight expansion of the lung which could be explained as
 due to the more rapid diffusion of oxygen and carbon dioxid from
 the venous blood into the alveoli than of nitrogen into the blood.
 From these facts it can be deduced, that when after the introduction
 of pure nitrogen the oxygen and carbon dioxid have reached these
 figures the absorption of the alveolar gases from this point on should
 proceed at the same rate as if air were now present.

Results Following Introduction of Neutral Gases Separately into
 the Atelectatic Lung. Nitrogen, hydrogen and helium were the gases
 used in these experiments.

Dog 517. Closed-chest experiment. This animal weighed 11 kg. Sodium
 iso-amyl-ethyl barbituric anesthesia was used and the left lower lobe
 bronchus obstructed.

5.30 P.M.: The left lower lobe was atelectatic.

5.45 P.M.: 100 cc. of nitrogen was introduced.

9.35 P.M.: A specimen of gas contained 5.51 per cent oxygen and
 7.34 per cent carbon dioxid.

9.40 A.M. (next day): The lung was again atelectatic, showing that
 the nitrogen was completely absorbed in 16 hours.

Dog 515. Closed-chest experiment. This dog weighed 12.5 kg. Sodium
 iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was
 obstructed.

12.10 P.M.: The left lung was rendered atelectatic.

12.40 P.M.: 105 cc. of hydrogen was introduced.

4.30 P.M.: A specimen of alveolar air contained 6.16 per cent oxygen
 and 5.03 per cent carbon dioxid.

9.57 P.M.: A specimen of alveolar air contained 5.50 per cent oxygen
 and 6.38 per cent carbon dioxid.

6.00 A.M. (next day): Lung again atelectatic, showing that the absorp-
 tion time for hydrogen was 18 hours.

Dog 510. Closed-chest experiment. This dog weighed 22 kg. Sodium
 iso-amyl-ethyl barbituric anesthesia was given. The left stem bronchus
 was obstructed.

8.30 A.M.: Atelectasis was complete. 175 cc. of pure helium was intro-
 duced into the left lung.

9.30 A.M.: Gas analysis showed 5.83 per cent oxygen and 9.34 per cent carbon dioxide.

1.00 P.M.: Gas analysis showed 5.34 per cent oxygen and 6.22 per cent carbon dioxide.

2.10 P.M.: Gas analysis showed 5.25 per cent oxygen and 6.64 per cent carbon dioxide.

4.30 P.M. (next day): Lung almost but not completely atelectatic in 26 hours.

TABLE 3.—EXCHANGE OF ALVEOLAR GASES AS SHOWN BY CARBON DIOXIDE AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO AN OBSTRUCTED LOBE OF THE LUNG.

Gas.	Dog.	1930, May.	Description.	Time.	CO ₂ per cent.	O ₂ per cent.
Helium	507	22	Open-chest experiment; left lower lobe washed out 9 times with oxygen and allowed to become atelectatic; 150 cc. of helium was introduced into it at	2.00 P.M. 2.10 P.M. 5.45 P.M.	4.54 5.03	2.66* 2.83*
Helium oxygen	510	23	Closed-chest experiment; left lower lobe was obstructed and allowed to become completely atelectatic; 200 cc. of a mixture of equal volumes of helium and oxygen was then introduced into it at	5.50 P.M. 8.00 P.M.	5.86	8.29
Helium	This lobe was now washed out 3 times with pure helium and 175 cc. of helium was introduced into it at	8.30 P.M. 9.30 P.M.	9.34	5.83
			The next day at	1.00 A.M. 2.10 A.M.	6.22 6.64	5.34 5.25
Hydrogen	515	27	Closed-chest experiment; left lower lobe was washed out 7 times with oxygen and allowed to become atelectatic; then 105 cc. of hydrogen was introduced into it at	12.40 P.M. 4.30 P.M. 9.57 P.M.	5.03 6.38	6.16 5.50
Nitrogen	517	27	Closed-chest experiment; left lower lobe was obstructed and washed out 3 times with nitrogen by aspiration and distending it with pure nitrogen after each aspiration; then 100 cc. of nitrogen was introduced into it at	5.45 P.M. 9.35 P.M.	7.34	5.51*

* These are unusually low figures for alveolar oxygen, probably due to poor respiration and anoxemia.

Table 3 is a résumé of these experiments.

The foregoing experiments show that a short while after the introduction of neutral gases into the atelectatic lung oxygen and

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sis showed 5.83 per cent oxygen and 9.34 per cent carbon dioxide. The blood showed 5.34 per cent oxygen and 6.22 per cent carbon dioxide. The blood showed 5.25 per cent oxygen and 6.64 per cent carbon dioxide. Lung almost but not completely atelectatic in 26

ALVEOLAR GASES AS SHOWN BY CARBON DIOXID AND OXYGEN AFTER INTRODUCTION OF VARIOUS GASES INTO OBSTRUCTED LOBE OF THE LUNG.

Description.	Time.	CO ₂ per cent.	O ₂ per cent.
Open-chest experiment; left lower lobe washed out 9 times with oxygen and allowed to become atelectatic; 150 cc. of helium was introduced into it at	2.00 P.M. 2.10 P.M. 5.45 P.M.	4.54 5.03	2.66* 2.83*
Open-chest experiment; left lower lobe was obstructed and allowed to become completely atelectatic; 150 cc. of a mixture of equal volumes of helium and oxygen was introduced into it at	5.50 P.M. 8.00 P.M.	5.86	8.29
Open-chest experiment; left lower lobe was now washed out 3 times with pure helium and 175 cc. of oxygen was introduced into it at	8.30 P.M. 9.30 P.M. 1.00 A.M. 2.10 A.M.	9.34 6.22 6.64	5.83 5.34 5.25
Open-chest experiment; left lower lobe was washed out 7 times with oxygen and allowed to become atelectatic; then 105 cc. of hydrocarbon gas was introduced into it at	12.40 P.M. 4.30 P.M. 9.57 P.M.	5.03 6.38	6.16 5.60
Open-chest experiment; left lower lobe was obstructed and washed out 10 times with nitrogen by aspiration and distending it with pure oxygen after each aspiration; 10 cc. of nitrogen was introduced into it at	5.45 P.M. 9.35 P.M.	7.34	5.51

figures for alveolar oxygen, probably due to poor

these experiments.

These experiments show that a short while after the gases enter the atelectatic lung oxygen and

PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION 337

Carbon dioxide diffuses through the alveolar membrane from the venous blood so that these gases are present in the alveoli under the same partial pressures as in the blood, as previously mentioned. When a mixture of equal parts of a neutral gas and oxygen or carbon dioxide is introduced into the atelectatic lung the same phenomenon of rapid establishment of gas equilibrium occurs.

Dog 510.

5.50 P.M.: 200 cc. of equal parts of helium and oxygen by volume were introduced into the atelectatic left lung.

7.20 P.M.: Gas analysis showed 5.86 per cent oxygen and 8.29 per cent carbon dioxide.

The same modifications in the percentages of alveolar gaseous content occur when active gases (oxygen, carbon dioxide) are introduced individually into the atelectatic lung.

Dog 498. *Open-chest experiment.* This dog weighed 6.5 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was obstructed and rendered atelectatic.

10.40 P.M.: 100 cc. of oxygen was introduced into the atelectatic lower left lobe.

10.50 P.M.: Gas analysis showed 8.59 per cent oxygen and 8 per cent carbon dioxide.

If an acute pathologic alteration of the lung endothelium is produced so that the respiratory membrane loses its permeability or the capillaries are damaged atelectasis does not occur. This is shown in a remarkable way when ether in 100 per cent concentration is introduced into the atelectatic lung. Undiluted ether vapor can be rapidly absorbed (100 cc. in 1 minute), but more often it produces a hemorrhagic edema (Fig. 6) strictly limited to the obstructed portion of the lung. In these cases further introduction of gas in the lung, even of carbon dioxide, which is usually rapidly absorbed, is not followed by atelectasis. The lung has lost its functional ability for the exchange of gases through the alveolar and capillary endothelium. Production of atelectasis has become impossible. This fact is illustrated in experimental Dog 499 (open-chest), the protocol of which is given here.

Dog 499. This animal weighed 15 kg. 55 mg. of Sodium iso-amyl-ethyl barbituric per kilogram of body weight was given intraperitoneally.

April 30, 1930. 1.00 P.M.: The dog was in the oscillating negative pressure box (oscillations from -4 to -8). The oscillation rate was 14 per minute. The heart rate was 116. Temperature, 40° C. 1/4 grain (16 mg.) of ephedrin sulphate was given hypodermically. The left lung was obstructed and washed out with oxygen.

4.15 P.M.: There was complete atelectasis of the entire left lung.

4.21 P.M.: Carbon dioxide was introduced to distend the left lung (about 300 cc.).

4.24 P.M.: The carbon dioxide was completely absorbed and there was total atelectasis again.

4.41 P.M.: 100 per cent ether vapor was introduced to distend the lung to the size previously obtained with carbon dioxide (ether vapor was obtained by slowly passing liquid ether through a long metallic coil immersed in water at 90° C.).

4.45 P.M.: The left lung became edematous, of a dark pink to red color and larger than the atelectatic lung was at 4.24 P.M.

4.47 P.M.: Oxygen was introduced into the left lung to distend it to its former size.

5.02 P.M.: There was no apparent absorption; the volume of the lung was the same.

5.06 P.M.: The clamp on the lung catheter was removed. A strong odor of ether came out of the catheter in a forceful stream of gas; the whole amount of oxygen introduced was withdrawn, showing that none of the oxygen and not all of the ether had been absorbed.

Postmortem. The left lung was pinkish red; in section it was very hemorrhagic and edematous. The weight of the right lung was 140 gm.; of the left (edematous) lung, 232 gm. Microscopic section showed interstitial hemorrhage and edema.

Table 4 shows absorption times of ether in 2 experiments.

TABLE 4.—ETHER ABSORPTION TIMES.

Animal.	Weight, kg.	Volume, ether vapor.	Absorption time, min.
498	10	150	1
504	12	200	3

It is seen that 100 per cent ether vapor is quickly absorbed by the lung in each case, but often after the first introduction and always after a subsequent one it rapidly produces a hemorrhagic edema of the obstructed lobe, so that the lobe in question has lost its functional ability to absorb any gas or vapor which may be introduced into it from now on.

Tables 5 and 6 are summaries of a closed and open chest experiment, using various gases successively in a lower lobe.

TABLE 5.—ANIMAL 511. CLOSED-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	230	23
Oxygen	275	15
Ethylene	250	25
Oxygen	230	14
Carbon dioxide	275	5
Ethylene	275	15
Oxygen	275	12
Carbon dioxide	250	3
Nitrous oxid	250	17
Nitrous oxid	250	22

It will be noted that the absorption times in the open-chest run higher than for the closed-chest. This is probably due to the fact that fluoroscopic observation through the chest is not delicate enough to allow detection of the end point of absorption; that is,

ether vapor was introduced to distend the lung with carbon dioxide (ether vapor was obtained through a long metallic coil immersed in

became edematous, of a dark pink to red color. The lung was at 4.24 P.M.

introduced into the left lung to distend it to its

apparent absorption; the volume of the lung

the lung catheter was removed. A strong odor of ether in a forceful stream of gas; the whole was withdrawn, showing that none of the ether had been absorbed.

It was pinkish red; in section it was very hemorrhagic. The weight of the right lung was 140 gm.; of the left 120 gm. Microscopic section showed interstitial

absorption times of ether in 2 experiments.

—ETHER ABSORPTION TIMES.

Weight, kg.	Volume, ether vapor.	Absorption time, min.
10	150	1
12	200	3

cent ether vapor is quickly absorbed by the lung. It often after the first introduction and the second it rapidly produces a hemorrhagic edema, so that the lobe in question has lost the ability to absorb any gas or vapor which may be introduced.

Results of a closed and open chest experiment successively in a lower lobe.

511. CLOSED-CHEST EXPERIMENT.

Volume.	Absorption time, min.
280	23
275	15
250	25
280	14
275	5
275	15
275	12
250	3
250	17
250	22

absorption times in the open-chest run. This is probably due to the fact that the introduction through the chest is not delicate at the end point of absorption; that is,

after the great bulk of gas is absorbed further shrinkage of the lung and absorption of the minimal remnants cannot be followed by fluoroscope. (Figs. 3, 5A and 5B.) In the open-chest experiment absorption of the last traces of gas can be observed directly.

TABLE 6.—ANIMAL 504. OPEN-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	175	35
Carbon dioxide	175	17
Ethyl chlorid	175	10
Ethylene	175	29
Carbon dioxide	200	21
Ethyl chlorid	500	17
Carbon dioxide	300	42
Ethylene	300	13
Oxygen	300	19
Ether	200	3

From Table 5 it might appear that nitrous oxid and ethylene are innocuous to the pulmonary endothelium; even with repeated introduction their absorption times as well as those of oxygen and carbon dioxide are not prolonged. It should be remarked, however, that with nitrous oxid 5 cc. of serous fluid was obtained from the lobe of lung 11 minutes after its introduction and 1 cc. of serous fluid 22 minutes after its introduction. With ethylene 24 cc. of serous fluid could be withdrawn from lung 1½ hours after introduction of the gas. This probably indicates the irritating effect of one or both gases. After the second introduction of ethylene 10 cc. of gas could still be withdrawn 2½ hours after its introduction and yet fluoroscopy showed the appearance of the lung to be the same as at 15 minutes after introduction. It would appear then, that the great mass of ethylene (and also nitrous oxid) is absorbed quite readily, but that later with the lung almost atelectatic the absorption process is much slower, possibly due, for one thing, to a combination of impoverishment of capillary circulation in the collapsed state and, on the other hand, to a slight degree of endothelial damage. Considering the figures of the table, and that 100 per cent concentration of gases were used, it is likely that nitrous oxid and ethylene in concentrations usually used in anesthesia are fairly innocuous to the lung. The experiments cited for 100 per cent concentration of ether vapor show it to be much more irritating, hemorrhagic edema, as a rule, being produced, so that high concentrations of ether in anesthesia are to be particularly avoided. From Table 5 we saw that even assuming very slight endothelial damage, the successive absorption times for the great mass of gases were not materially lengthened by nitrous oxid and ethylene introduction. In Table 6 the first carbon dioxide introduction after the first nitrous oxid introduction was followed by atelectasis in 17 minutes, as compared to 3 to 5 minutes for carbon dioxide in Table 5. We

should probably deduce from Table 6 that nitrous oxid introduction was the cause of the lengthening of the carbon dioxid absorption time. However, Table 5 does show that *successive* introductions of ethylene and nitrous oxid did not prolong the absorption times of gases subsequently introduced. In Table 6 it is seen that the absorption times for carbon dioxid at successive introductions were relatively increased, being 17, 21 and 42 minutes respectively. Since the new factor introduced in Table 6 is ethyl chlorid, this may point to the deleterious effect of 100 per cent concentration of ethyl chlorid vapor on the endothelium. This effect does not appear to be permanent, for the larger second volume of ethylene following ethyl chlorid took only 29 minutes to absorb; later, ethylene following the second ethyl chlorid introduction took only 13 minutes, possibly because of the beneficial effect of the intervening carbon dioxid introduction. That the ethyl chlorid effect is not permanent is shown by the fact that the final oxygen introduced took only 19 minutes to absorb, about the average normal period. On the contrary, the ether vapor effect appears to be permanent.

TABLE 7.—AVERAGES OF ABSORPTION TIMES OF GASES FROM A LUNG INFLATED TO FULL INSPIRATORY STATE.

Oxygen	15 min.	Nitrous oxid	17 to 35 min.
Carbon dioxid	4 "	Ethylene	13 to 29 "
Nitrogen	16 hrs.	Ethyl chlorid	10 to 17 "
Hydrogen	18 "	Ether	1 to 3 "
Helium, over	26 "		

For the sake of completeness, it is of interest to compare the absorption times of air, nitrogen, oxygen, carbon dioxid, hydrogen and helium in the pleural cavity, with those for the lung; for the pleura is a closed cavity completely lined with an endothelial membrane, permeable to gases, over half of which is in close relation to the capillary system of the lung. Therefore, it would not be surprising if gas absorption in the pleural cavity were accomplished according to the same laws which regulate gas absorption in an alveolus completely closed off by bronchial obstruction. This conception which will be elaborated in a forthcoming paper on gas behavior in the human pleura justifies the presentation of the data to follow.

Behavior of Gases in the Pleural Cavity. Some preliminary observations were carried out in rabbits, rather than the dog, for they have a mediastinum which is much more comparable to that in the human. The mediastinum of the dog is a flimsy structure which is permeable to gases and fluids so that a unilateral pneumothorax is not possible. On the contrary, in rabbits a measured volume of gas can be introduced into the pleural cavity of one side and unilateral pneumothorax produced. Its absorption is followed by observing the degree of return of the heart and mediastinum

from Table 6 that nitrous oxid introduction lengthening of the carbon dioxid absorption does show that successive introductions of did not prolong the absorption times of reduced. In Table 6 it is seen that the on dioxid at successive introductions were ng 17, 21 and 42 minutes respectively. reduced in Table 6 is ethyl chlorid, this ous effect of 100 per cent concentration of endothelium. This effect does not appear larger second volume of ethylene following minutes to absorb; later, ethylene follow- orid introduction took only 13 minutes, beneficial effect of the intervening carbon t the ethyl chlorid effect is not permanent t the final oxygen introduced took only out the average normal period. On the effect appears to be permanent.

ABSORPTION TIMES OF GASES FROM A LUNG INFLATED
FULL INSPIRATORY STATE.

5 min.	Nitrous oxid . . .	17 to 35 min.
1 "	Ethylene . . .	13 to 29 "
6 hrs.	Ethyl chlorid . . .	10 to 17 "
"	Ether . . .	1 to 3 "

teness, it is of interest to compare the trogen, oxygen, carbon dioxid, hydrogen cavity, with those for the lung; for the completely lined with an endothelial ases, over half of which is in close rela- n of the lung. Therefore, it would not tion in the pleural cavity were accom- me laws which regulate gas absorption osed off by bronchial obstruction. This aborated in a forthcoming paper on gas ra justifies the presentation of the data

the Pleural Cavity. Some preliminary ut in rabbits, rather than the dog, for hich is much more comparable to that stinum of the dog is a flimsy structure and fluids so that a unilateral pneumo- the contrary, in rabbits a measured uced into the pleural cavity of one side produced. Its absorption is followed return of the heart and mediastinum

back to their normal position as checked up by fluoroscopy and Roentgen ray. (Figs. 7A and 7B.)

The gases used were air, nitrogen, oxygen, carbon dioxid, hydro- gen and helium. In each case 75 cc. were introduced into the pleural cavity of a rabbit weighing about 2 kg., and the absorption times studied by fluoroscopy and Roentgen ray. (Table 8.) This volume of gas produced a very marked shift of the heart to the opposite side. (Figs. 7A and 7B.) In 3 experiments carbon dioxid, oxygen and nitrogen were introduced into the pleura and samples of gas later removed for analysis of their carbon dioxid and oxygen contents. In this way some insight into the nature of gas exchanges through the pleura was to be had.

TABLE 8.—ABSORPTION TIMES OF GASES INTRODUCED INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	June, 1930.	Rabbit.	Volume gas introduced, cc.	Pleural cavity.	Absorption time.
Air	4	18	75	Right	6 days
Nitrogen	4	14	75	Right	6 "
	16	16	75	Right	6 "
Oxygen	11	16	75	Left	2 hrs.* for 40 cc.
Carbon dioxid	11	14	75	Left	5 min.
Hydrogen	4	17	75	Right	4 days
Helium	4	16	75	Right	4 "
"	16	14	75	Right	4 "

* 35 cc. of gas were withdrawn for determination of carbon dioxid and oxygen percentages.

TABLE 9.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	Rabbit	Date.	Description.	Time.	CO ₂ , per cent.	O ₂ , per cent.	N ₂ , per cent (by subtraction).
Carbon dioxid.	19	May 11, 1930	75 cc. carbon dioxid in right pleural cavity at Gas sample at	11:00 P.M. 11:08 A.M.	90.00	1.50	8.50
Oxygen	16	May 11, 1930	75 cc. oxygen in left pleural cavity at Gas sample at Gas sample at	2:40 P.M. 3:00 P.M. 4:40 P.M.	6.53 6.52	93.40 93.44	Trace Trace
Nitrogen	18	June 11, 1930	75 cc. nitrogen in left pleural cavity at Gas sample at Gas sample next day at	3:55 P.M. 4:15 P.M. 8:30 P.M.	4.67 5.89	3.67 9.90	91.66 84.41

Table 8 is a summary of pleural absorption times. In the pleura, as in the lung, the times of absorption for the inert gases, nitrogen,

hydrogen, helium, and for air are relatively high, as in the lung, oxygen and carbon dioxid have comparatively short absorption times.

TABLE 10.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF CARBON DIOXID INTO THE PLEURAL CAVITY OF THE DOG.

Gas.	Dog.	Date.	Description.	Time after introduction.	CO ₂ per cent.	O, per cent.	N, per cent (by subtraction).
Carbon dioxid	671	May 9, 1931	250 cc. CO ₂ introduced into right pleural cavity at . .	11.50 A.M. 3 min. 15 min. 1 hr., 7 min. 2 hrs., 20 min.	96.00 69.4 10.9 6.4	1.5 10.2 15.2 14.1	2.5 20.4 73.9 79.5

TABLE 11.—SUMMARY OF SOLUBILITY COEFFICIENTS AND ABSORPTION TIMES OF VARIOUS GASES.

Gas.	Density, gm. per 1000 cc.	Molecular weight.	Solub., gm. per 100 gm. H ₂ O.	Temp.	Solub. coeff., cc. gas sol. in 1 cc. H ₂ O.	Absorption time.	
						Pleura* (rabbit).	Lung† (dog).
Air	1.30	..	0.004	35° C.	0.015	6 days	16 hrs.
Nitrogen	1.25	28	0.003	35° C.	0.012	6 days	16 hrs.
Oxygen	1.43	32	0.007	35° C.	0.024	2 hrs.	15 min.
Carbon dioxid	1.98	44	0.330	35° C.	0.592	5 min.	4 "
Hydrogen	0.09	2	0.00025	35° C.	0.016	4 days	18 hrs.
Helium	0.18	4	0.00020	25° C.	0.014	4 "	26 "
Nitrous oxid	1.95	44.20	0.067‡	37° C.	0.326	..	17 to 35 min.
Ethylene	1.27	28.03	0.010‡	37° C.	0.080	..	13 to 29 "
Ethyl chlorid vapor	2.86	64.50	0.878§	37° C.	3.07	..	10 to 17 "
Ether vapor	3.11	74	4.962§	37° C.	15.94	..	1 to 3 "

* 75 cc. of gas introduced into pleural cavity.

† Enough gas to inflate one lobe to full inspiratory state.

‡ Volumetrically determined by us with the eudiometer.

§ Gravimetrically determined by us.

Gas Exchanges in the Pleura.—In Table 9 the pleural gas exchanges following introduction of carbon dioxid, oxygen and nitrogen in the pleura of rabbits are given. When carbon dioxid was introduced into the pleura gas analysis 6 minutes later showed that 1.5 per cent O₂ and 8.5 per cent N₂ had diffused into the pleural cavity. Due to the very rapid absorption of CO₂ in the rabbit, analysis of the pleural gases over an appreciable period was found impossible. For this reason 250 cc. of CO₂ was introduced into the right pleural cavity of a dog weighing 10 kg. (Table 10.) Owing to the flimsy mediastinum of the dog, which is permeable to gases, a bilateral pneumothorax was thus produced, and 20-cc. samples of pleural gas were withdrawn for analysis over a period of 2 hours

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for air are relatively high, as in the lung, and have comparatively short absorption times.

EXCHANGE OF GASES AS SHOWN BY CARBON DIOXIDE MINERATIONS AFTER INTRODUCTION OF CARBON IN THE PLEURAL CAVITY OF THE DOG.

Description.	Time after introduction.	CO ₂ per cent.	O ₂ per cent.	N ₂ per cent (by subtraction).
Gas introduced into pleural cavity at 11.50 A.M.				
	3 min.	96.00	1.5	2.5
	15 min.	69.4	10.2	20.4
	1 hr., 5 min.	10.9	15.2	73.9
	2 hrs., 20 min.	6.4	14.1	79.5

SOLUBILITY COEFFICIENTS AND ABSORPTION TIMES OF VARIOUS GASES.

Solub. coeff. 100 gm. H ₂ O.	Temp.	Solub. coeff. cc. gas sol. in 1 cc. H ₂ O.	Absorption time.	
			Pleura* (rabbit).	Lung† (dog).
0.004	35° C.	0.015	6 days	16 hrs.
0.003	35° C.	0.012	6 days	16 hrs.
0.007	35° C.	0.024	2 hrs.	15 min.
0.330	35° C.	0.592	5 min.	4 "
0.00025	35° C.	0.016	4 days	18 hrs.
0.00020	25° C.	0.014	4 "	26 "
0.067	37° C.	0.326	..	17 to 35 min.
0.010	37° C.	0.080	..	13 to 29 "
0.878	37° C.	3.07	..	10 to 17 "
4.962	37° C.	15.94	..	1 to 3 "

* In pleural cavity.
† In full inspiratory state.
by us with the eudiometer.
by us.

pleura. In Table 9 the pleural gas exchanges of carbon dioxide, oxygen and nitrogen in the pleura. When carbon dioxide was introduced into the pleural cavity 6 minutes later showed that 1.5 per cent N₂ had diffused into the pleural cavity. Absorption of CO₂ in the rabbit, analysis of an appreciable period was found impossible. 55 cc. of CO₂ was introduced into the right pleural cavity of a dog weighing 10 kg. (Table 10.) Owing to the fact that the dog, which is permeable to gases, as thus produced, and 20-cc. samples of blood were taken for analysis over a period of 2 hours

and 20 minutes after introduction of carbon dioxide. Two hours and 45 minutes after introduction 55 cc. of gas could still be withdrawn from the right pleural cavity. Table 10 shows a progressive fall in CO₂ percentage and rise in O₂ and N₂ percentages, the last reading showing 6.4 per cent CO₂, 14.1 per cent O₂ and 79.5 per cent N₂, or approximately the composition of alveolar air or of the gases in arterial blood. We are as yet unable to state definitely the relative importance of the visceral and parietal pleura in the pleural exchange and final equilibrium of gases. This phase of the subject is still under investigation.

When oxygen was introduced into the pleura, analysis 20 minutes later showed a carbon dioxide percentage of 6.53 and an oxygen percentage of 93.4. Gas analysis 1 hour and 40 minutes later showed practically the same percentages. Carbon dioxide had therefore diffused into the pleural cavity and was present at about venous blood concentration. (Table 9.) Only traces of nitrogen had diffused into the pleural cavity. An equilibrium thus tended to be established; a perfect equilibrium is never obtainable so long as the absorbing power of the pleura is unimpaired. The constant imbalance and continuously changing partial pressures of gases or vapors on opposite sides of an absorbing membrane can account for this lack of equilibrium. Aside from this factor, in considering the rapidity of absorption and diffusion of gases through living membranes or tissues, an analogy is to be found *in vitro* in the diffusion of gases from one side of a membrane and through it into a stream of running water rather than into a beaker of water. A fresh stream of blood, arriving as it does in a relatively unsaturated state, is available to dissolve and continuously to carry away gases or vapors from the pleura or lung.

When nitrogen was introduced there was a diffusion of nitrogen out of, and oxygen and carbon dioxide into the pleural cavity. Gas analysis 20 minutes after the introduction of nitrogen showed that 4.67 per cent of carbon dioxide and 3.67 per cent oxygen had diffused into the pleural cavity. These percentages were obviously below equilibrium points because gas analyses 28 hours later showed carbon dioxide had risen to 5.69 and oxygen to 9.9. The latter figure for oxygen, which is between the venous oxygen concentration (5 per cent) and arterial concentration (14 per cent), may indicate that a further rise of oxygen percentage would have been found in subsequent analyses, or else that oxygen in the pleura now tended to be in equilibrium with arterial blood.

Pleural Absorption Compared to Pulmonary Absorption. From Table 11 it will be noted that in the pleura, as well as in the lung, air, nitrogen, hydrogen and helium require a long period for absorption compared to oxygen and carbon dioxide; for the former gases are dependent chiefly on their degree of solubility in the moist endothelium and blood for absorption from the lung. That the

density, and therefore diffusibility, has very little to do with the time of absorption of an inert gas, is clearly demonstrated in the case of nitrogen and hydrogen which are about equally soluble in water. Nitrogen with a molecular weight of 28 is 14 times as dense as hydrogen with a molecular weight of 2. Nitrogen, therefore, has only about $0.26 \left(\frac{1}{\sqrt{14}} \right)$ the diffusion speed of hydrogen and

should, theoretically, require 4 times as long to absorb as does hydrogen; yet in the pleura nitrogen required only 1.5 times as long a period to absorb as did the hydrogen. In the lung, nitrogen and hydrogen were absorbed in approximately equal times. Although the solubility coefficients of oxygen and carbon dioxide are respectively 2 times and 50 times that of nitrogen (Tables 8 and 10), the former two gases were absorbed from the lung and pleura in far less than one-half and one-fiftieth the time for nitrogen. As previously mentioned in the case of oxygen and carbon dioxide, the factors of affinity of carbon dioxide for alkalies of the tissues and blood and of oxygen for hemoglobin account for rapid absorption of these gases as compared with nitrogen, hydrogen, helium and air. These factors appear to obtain both for the pleural cavity and the lung. Carbon dioxide is apparently quite as rapidly absorbed from the pleura as from the lung. Oxygen would appear to be slower in absorption from the pleura, and the inert gases, nitrogen, hydrogen, helium and air require considerably longer times for pleural absorption.

It would not, however, appear surprising for the pulmonary absorption of a gas to be more rapid than pleural absorption; in fact, it is rather to be expected. The construction of the lung is ideal for gas absorption, the myriads of alveoli offering a large absorbing surface (a maximum of 1000 square meters) for the gases contained within them. Each alveolus is surrounded by a rich capillary network in intimate contact with the very thin pulmonary endothelium through which a rapid interchange of gases can take place. As compared with the pulmonary endothelium the pleura offers a relatively small absorbing surface for the volume of gas introduced into the pleural cavity; it is not endowed with a highly specialized capillary network such as is found around each alveolus. It seems reasonable to deduce, therefore, that the most of the absorption is carried out by the visceral pleura, notwithstanding the lung's decrease in surface and the impaired circulation due to collapse of the underlying pulmonary tissue. This may be why the rate increases as the lung expands (improved pulmonary alveolar circulation) and decreases as the pleura thickens. On this important point studies on the human are being carried out at Metropolitan Hospital, Tuberculous Service, New York City.

In a general way Table 11 shows that both for gases and anesthetic vapors the absorption times for the lung are inversely proportional to the solubility coefficients of the gases and vapors studied. This

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The construction of the lung is ideal iads of alveoli offering a large absorbing) square meters) for the gases contained is is surrounded by a rich capillary net h the very thin pulmonary endothelium erchange of gases can take place. As nary endothelium the pleura offers a rface for the volume of gas introduced not endowed with a highly specialized found around each alveolus. It seems fore, that the most of the absorption al pleura, notwithstanding the lung's impaired circulation due to collapse of sue. This may be why the rate increases ed pulmonary alveolar circulation) and ens. On this important point studies arried out at Metropolitan Hospital, ork City.

hows that both for gases and anesthetic for the lung are inversely proportional f the gases and vapors studied. This

is shown by taking the solubility coefficient of nitrogen, an inert gas, as a standard, and comparing to it the solubility coefficient of the gas or vapor in question, remembering that the higher the solubility coefficient, the quicker is the absorption. Oxygen and even the highly soluble carbon dioxid are noticeable exceptions to the rule. The affinity of carbon dioxid for alkali of the tissues and blood and of oxygen for hemoglobin, already pointed out, account for the relatively rapid absorption of these gases from the pleural cavity and lung.

Ethylene required a much shorter time for absorption and ethyl chlorid vapor and helium a little longer time for absorption than calculated from the water solubility coefficients of these gases. Ether vapor was absorbed most rapidly of all, as would be expected from its high solubility coefficient, in spite of the fact that its diffusibility is least of all the vapors and gases studied (because of its high density); its absorption time is in agreement with the findings of Van Mechelen,¹¹ who showed ether to be absorbed from the human lung with great rapidity. He found that on inhalation of $1\frac{1}{2}$ liters of air containing from 9 to 26 per cent ether (26 to 78 gm. per 100 liters air) over 95 per cent of the ether was absorbed from the human lung in 2 seconds. Van Mechelen found that ether was in some instances considerably less soluble in blood than in distilled water. However, there are two other factors aside from the high solubility of ether which can account for the rapid absorption of ether from the lung. The first is that arterial blood (carotid artery) in a single and first passage through a lung containing about 14 per cent ether became two-thirds saturated with this anesthetic. The second point is that Van Mechelen showed the arterial blood to contain considerably more ether than the venous blood even after more than 3 hours of anesthesia. The venous blood thus remains relatively unsaturated by ether for long periods and so can absorb considerable volumes of ether vapor as it courses through the lung again and again. In the light of these considerations the rapid absorption of ether from the lung becomes clear.

A point of interest is the cause and mechanism of the possible irritant or even corrosive action of strong concentrations of ether vapor in the lung. As previously stated, 100 per cent concentration ether vapor often produced hemorrhagic edema of the lung in our experimental animals. A possible contributory cause of this may lie in the fact, as we have found, that ether containing traces of water may exist as a liquid at body temperature ($37^{\circ}\text{C}.$), whereas pure ether boils at $34.5^{\circ}\text{C}.$ and can exist only as a vapor at body temperature. Moreover when water is dissolved in ether to the extent of 9.92 to 100 gm. of ether (0.09 gm. H_2O per gm. ether) a perfect solution is obtained, which does not boil below $45^{\circ}\text{C}.$ Due to water vapor in the lung and water in the endothelium itself, it is conceivable, therefore, in view of what we have just said, that

ether in high concentrations in the lung may condense and remain as a liquid on the pulmonary endothelium. Such liquid ether might irritate pulmonary tissue first by its dehydration of the endothelium and then by a direct action upon it. This could account for the hemorrhagic edema produced by high concentrations of ether vapor in the lung.

Summary and Conclusions. Gases and anesthetic vapors contained in alveolar cavities shut off by complete bronchial obstruction gradually leave the lung and finally disappear so that the lung becomes atelectatic.

The speed of the disappearance of these gases is proportionate to their solubility coefficient, diffusion speed and to their chemical affinities for substances dissolved in the blood (hemoglobin in the case of oxygen, alkalies in the case of carbon dioxide, etc.).

Since ligation of the branches of the pulmonary artery corresponding to the obstructed lung prevent this disappearance of gases and vapors from the alveoli (Lichtheim, Schlaepfer), it has been concluded that this disappearance is due to absorption by the blood circulating through the lung. However, no direct evidence of this contention has ever been presented.

In this paper a detailed study has been presented of the times of absorption of oxygen, carbon dioxide, nitrogen, hydrogen and helium introduced into a lung previously rendered atelectatic. In this way the absorption times have been determined with considerable accuracy and their absorption has been proven.

Determinations which were carried out by the same technique for anesthetic vapors and gases, namely, ether, ethyl chlorid, nitrous oxide and ethylene showed the great rapidity of their absorption.

Integrity of the alveolar endothelium is just as necessary as integrity of the pulmonary circulation. Edema of the lung produced by injection of concentrated ether vapor into the lung instantaneously stops gas absorption.

Comparative study of absorption by the pleural cavity of oxygen, carbon dioxide, nitrogen, air, hydrogen and helium showed that their absorption is regulated by the same physicochemical laws governing absorption of gases from the obstructed lung.

On the basis of the above experimental findings it has been endeavored to justify our contention that atelectasis always follows complete bronchial obstruction and that it cannot occur without complete bronchial obstruction.

The aim of this investigation has been to offer a direct experimental proof that complete bronchial obstruction is the exclusive cause of atelectasis.

In the third paper of these series a new theory of production of atelectasis will be given.

NOTE.—We are indebted to Mrs. Aies Larsen for preparation of histologic sections, to Miss Helen C. Warny of the Airo-Balloon Company, New York City, for a supply of helium gas, and to Mr. Eugene Ostrow for technical assistance.

CORYLLOS, BIRNBAUM:

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disappearance of these gases is proportionate to their diffusion speed and to their chemical solubility in the blood (hemoglobin in the case of carbon dioxide, etc.).

Changes of the pulmonary artery circulation in the lung prevent this disappearance of gases (Lichtheim, Schlaepfer), it has been concluded that the disappearance is due to absorption by the blood. However, no direct evidence of this has been presented.

A study has been presented of the times of disappearance of carbon dioxide, nitrogen, hydrogen and helium previously rendered atelectatic. In this study it has been determined with considerable accuracy that absorption has been proven.

Experiments were carried out by the same technique for various gases, namely, ether, ethyl chlorid, nitrous oxide, the great rapidity of their absorption by the pulmonary endothelium is just as necessary as the rapidity of their circulation. Edema of the lung produced by ether vapor into the lung instantly.

Absorption by the pleural cavity of oxygen, hydrogen and helium showed that the same physicochemical laws governing absorption in an obstructed lung.

From the above experimental findings it has been concluded that atelectasis always follows bronchial obstruction and that it cannot occur without bronchial obstruction.

Attention has been to offer a direct experimental proof that bronchial obstruction is the exclusive cause of atelectasis.

In this series a new theory of production of atelectasis is presented.

A. J. Larsen for preparation of histologic sections, Airo-Balloon Company, New York City, for Eugene Ostrow for technical assistance.

PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION 347

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*

III. A THEORY OF AIR ABSORPTION IN ATELECTASIS.

By POL. N. CORYLLOS, M.D.,

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(From the Department of Surgical Research, Cornell University Medical College, New York.)

CONSIDERATIONS brought forth in the previous papers of this series lead us to the conclusion that atelectasis is the end result of the interchange between the gases of the alveoli and the perialveolar capillary blood through the pulmonary endothelium. Atelectasis must inevitably follow complete bronchial obstruction as a result of the absorption of the alveolar gases; conversely atelectasis cannot occur unless the alveolar gases are completely shut off from the external air. Incomplete obstruction of a bronchus would mean a renewal by the inspired air of the gases depleted in alveolar absorption.

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In the light of this theory atelectasis depends upon the difference in partial pressures of the gases on either side of this membrane upon the integrity of the pulmonary endothelium and upon the integrity of the pulmonary circulation allowing the gases absorbed from the alveoli to be carried away from the lung by the blood. The most important factor in the accomplishment and regulation of this exchange of gases is the difference in partial pressures of the gases in the alveoli and perialveolar capillary blood. Paul Ber showed first that in the alveoli or in the blood it is not the total pressure of the gas mixture, but the partial pressure of each individual gas acting as if it were alone which is of importance. In a

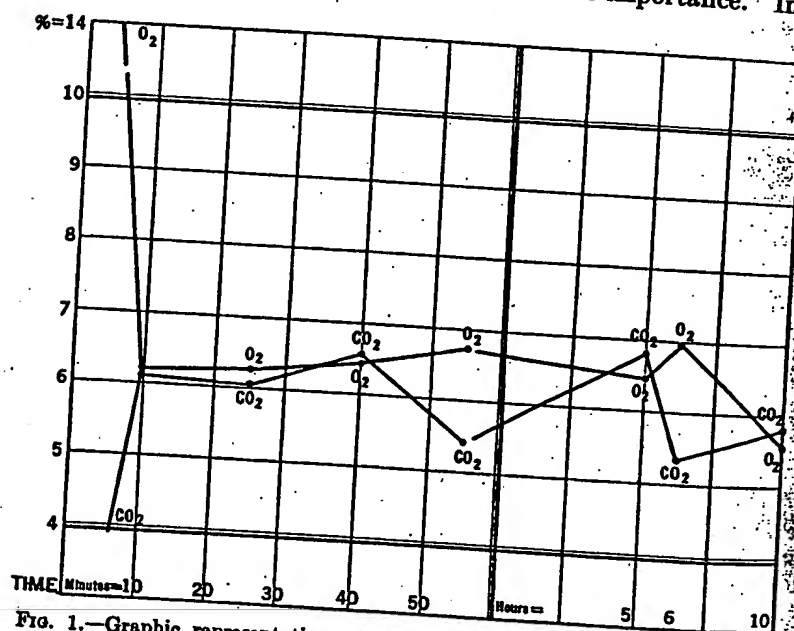
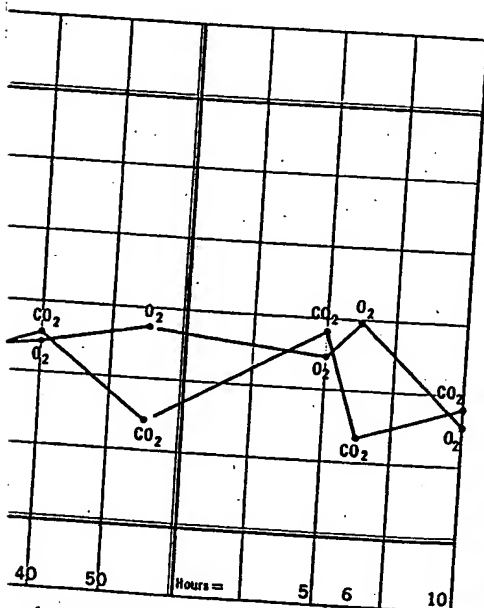


FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction of the right lung. Dog 482.

mixture of gases, where no chemical action occurs, each gas behaves independently; this fact is formulated in the law of partial pressures of Dalton. Thus, if 100 cc. of oxygen and 400 cc. of nitrogen both at one atmosphere of pressure are mixed, the resulting mass of gas occupies 500 cc. at the same pressure. Since equal volumes of gases at the same pressure contain equal numbers of molecules, the mixture contains 4 times as many nitrogen as oxygen molecules in the contained space. This means the nitrogen can exert 4 times as much pressure against a given membrane, for the bombardment and number of its molecules against it is 4 times as great as oxygen. Thus the oxygen acts as if it were under a pressure of only $\frac{1}{5}$ of an

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chemical action occurs, each gas behaves as if it were under a pressure of $\frac{1}{2}$ of an atmosphere ($\frac{1}{2} \times 760 = 380$ mm. Hg), while the nitrogen acts as if it were under a pressure of $\frac{1}{2}$ of an atmosphere ($\frac{1}{2} \times 760 = 380$ mm. Hg). Since equal volumes of gases contain equal numbers of molecules, the mixture of oxygen and 400 cc. of nitrogen both are mixed, the resulting mass of gas is under a pressure of 400 mm. Hg. Since the nitrogen can exert 4 times as great a pressure as oxygen, the bombardment against it is 4 times as great as oxygen. It is therefore under a pressure of only $\frac{1}{4}$ of an

atmosphere ($\frac{1}{4} \times 760 = 190$ mm. Hg), while the nitrogen acts as if it were under a pressure of $\frac{1}{2}$ of an atmosphere ($\frac{1}{2} \times 760 = 380$ mm. Hg).

In Fig. 1 is shown the percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction of a lobar bronchus and for a period of 10 hours thereafter. Within 10 minutes after obstruction the oxygen has fallen from 15 to 5 per cent and the carbon dioxide has gone from 5 to 6 per cent, showing that an approximate equilibrium with the venous alveolar capillaries has been established. From this point on, a series of gas exchanges takes place, leading ultimately, in 12 to 16 hours, to an atelectasis, as occurred in this case.

TABLE 1.—PERCENTAGES AND PARTIAL PRESSURES OF OXYGEN, CARBON DIOXIDE AND NITROGEN IN ALVEOLAR AIR AND VENOUS CAPILLARY BLOOD.

Gas.	Alveolar air.		Venous blood.	
	Per cent.	Partial pressure mm. Hg.	Per cent. of one atmosp.	Partial pressure, mm. Hg.
Oxygen	15	114	5	38.0
Carbon dioxide	5	38	6	45.6
Nitrogen	80	608	..	608.0

Table 1 represents in round figures the percentages of one atmosphere and the corresponding partial pressures of gases in the alveolar and venous air. These differences in partial pressures are possible notwithstanding the continuous exchange of gases through the respiratory membranes, only because the alveolar air is continuously renewed by respiration, by drawing by diffusion on the tidal air filling the bronchi on each respiration. This exchange is so active that in spite of the continuous renewal of air the alveolar air is poorer in oxygen and richer in carbon dioxide than the atmospheric air. It is precisely these differences in partial pressures between alveolar and venous gases which render possible oxygenation of the venous blood and elimination of its carbon dioxide.

It is obvious then that if a bronchus is obstructed the air entrapped in the lung will undergo qualitative changes. Its composition will gradually approach the percentages of the gases of the venous blood which is constantly coursing around the alveoli, carrying away gases which are under excess pressure in the alveoli (oxygen) and giving off gases to the alveoli which it has in excess (carbon dioxide). Such qualitative changes necessarily result in quantitative changes.

In order to simplify the question, we shall graphically represent the alveolus by a circle surrounded by a larger circle which represents the venous blood circulating in the perialveolar capillaries. (Fig. 2.) Further, 100 will represent the volumes of the air content of this alveolus (O₂ 15, CO₂ 5, N₂ 80). After obstruction of

the bronchiolus an equilibrium of gases inside and outside of the alveolus will be established. We shall consider the three gases separately.

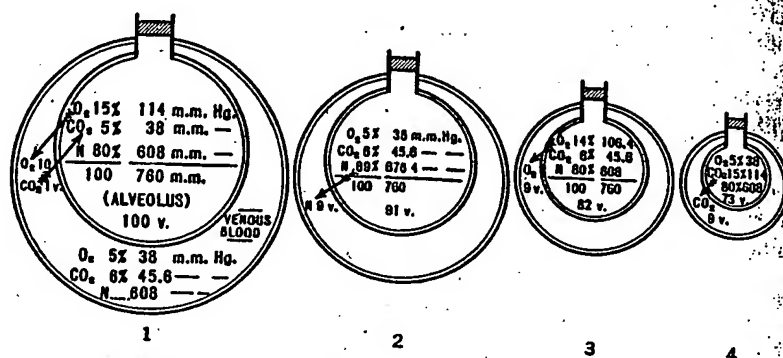
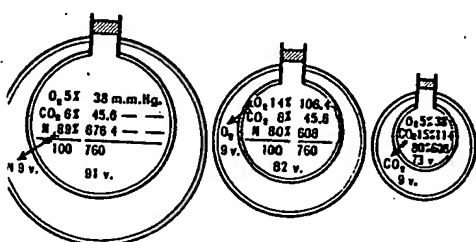


FIG. 2.—A schematic representation of alveolar gas exchanges, gradual gas absorption and shrinkage of the alveoli after complete bronchial obstruction. The absolute volume of the alveolus is only approximately indicated, but the figures are relative and demonstrate perfectly well the principles involved. In 1, 10 volumes of oxygen diffuse into the venous blood and 1 volume of carbon dioxide diffuses out of the venous blood and into the alveolus. In 2, the alveolus has now lost 9 volumes of gas as stated under 1 and oxygen and carbon dioxide have come into equilibrium in the venous capillary blood and in the alveolus. However, the percentage and partial pressure of nitrogen have now been increased so that 9 volumes of nitrogen diffuse out of the alveolus into the venous blood. In 3, 9 volumes of nitrogen having previously diffused out of the alveolus into the venous blood, the percentage and partial pressure of oxygen or carbon dioxide have been relatively increased. For purposes of explanation let us say the oxygen has thus been relatively increased in percentage and partial pressure. Nine volumes of oxygen are now ready to diffuse out of the alveoli into the venous blood. In 4, 9 volumes of oxygen having diffused from the alveolus into the blood, we can consider that the carbon dioxide in the alveolus is relatively increased by these 9 volumes. Thus the partial pressure of this gas is relatively increased and carbon dioxide is ready to diffuse out of the alveolus. Thus the cycle continues until all the gases of the lung are absorbed, although actually the gas exchanges are going on simultaneously and not in the isolated way which we have ideally considered.

Oxygen represents 15 per cent of the gas mixture, and it is under a partial pressure of 114 mm. of mercury in the alveolus, whereas in the venous blood it is present to the extent of 5 per cent of one atmosphere and a partial pressure of only 38 mm. of mercury. (Fig. 2.) Therefore, 10 volumes of oxygen will pass from the alveolus into the blood; at the same time, and for similar reasons, 1 volume of carbon dioxide will pass in the opposite direction from the blood to the alveolus. In this way the gas mixture of the alveolus will lose 9 per cent of its original volume, so that instead of 100 volumes there is now 91 volumes. Now if the alveolar wall were a rigid structure the total pressure of gas in the alveolus would decrease and instead of a pressure of $114 + 38 + 608 = 760$ mm. of mercury, it would become $38 + 45.6 + 608 = 671.6$ mm. of mercury. Since the alveolar wall is a perfectly elastic structure, it is obvious that the alveolus will retract because the pressure around it is 760 mm.

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of mercury. In fact the other lung being in connection with the
atmospheric air, the intrapulmonary pressure in it is 760 mm. of
mercury (the negative intrapleural pressure of from -4 to -7 mm.
of mercury is comparatively so small that it is of little importance
in this mechanism).

We shall now consider nitrogen. At the start, before bronchial
occlusion, it represented 80/100 of the alveolar gas mixture. Now
after the reduction in volume of the gas mixture it represents 80/91
of the gas mixture and its partial pressure has risen from 608 to
676.4 mm. of mercury. But this pressure is much higher than the
pressure of nitrogen in the capillary blood; the excess of nitrogen
will, therefore, pass into the blood. In other words, 9 volumes of
nitrogen will be carried from the alveolus by the circulating blood,
so that the volume of the alveolar air will be 91 - 9 = 82 volumes.*
(Fig. 2.)

This decrease in alveolar nitrogen disturbs again the equilibrium
of oxygen and carbon dioxide between the alveolar air and the venous
blood. Let us suppose that oxygen alone is affected by this imbalance.
It is obvious that instead of 5 per cent, as it was previously,
it will now represent 14 per cent of the alveolar gas mixture (N₂ 80
+ CO₂ 6 + O₂ 14 per cent) and, therefore, its partial pressure will
rise to 106 mm. of mercury; so that now again 9 volumes of oxygen
are ready to be carried away from the alveolus by the circulating
blood. When this happens the volume of the alveolus will decrease
to 82 - 9 = 73 volumes.

The carbon dioxide will be affected in the same way (Fig. 2), and
for similar reasons its percentage will rise from 6 to 15 per cent,
corresponding to a partial pressure of 114 mm. of mercury, so that
again 9 volumes of carbon dioxide are ready to be carried away by
the circulating blood, thus reducing the volume from 71 to 62.
The cycle is repeated, and 9 volumes of nitrogen will be ready to
pass from the alveolus into the venous blood. Continuing this
series of events, there will be a constant oscillation in gas values,
and all the alveolar gases will be absorbed. In the open chest
experiments we have noted that the initial absorption of gas is
slow; after a while the lung seems to shrink much more rapidly;
that is, there is an accelerated diminution in the size of the lung.
Toward the end of the process when the great mass of gas has already
been absorbed the process of absorption seems to slow down mark-
edly, so that one may observe small isolated or patchy areas remain-
ing practically unchanged over a long period of time. This mech-
anism is explained in Fig. 4, p. 332. The alveolus is represented by a

* These figures are not, strictly speaking, exact; for example, the volume of
nitrogen in Fig. 2 = 80/91 = 87.9/100 and the partial pressure corresponding to it
equals 667.04 mm. of mercury. We prefer to give the figures as they are, however,
because they simplify the explanation without altering any essential relations
between the gases.

sphere, the radius of which is 1. The ratio of surface to volume is 3 to 1. Now suppose gases are absorbed so that the alveolus shrinks and its radius is one-half; the ratio of surface to volume is now 6 to 1. In other words, the volume of contained gases has been diminished much more than the surface of the alveolus, and there is relatively twice as much surface for the contained volume of gas as there was previously. This means that there is more absorbing surface for a unit volume of gas, and the alveolus will absorb a greater fraction of its contained volume of gas per unit of time than in the previous case. Thus, with the progressive shrinkage of the lung there is an acceleration in the absorption rate. However, this effect is offset by the impoverishment of the capillary circulation when the alveoli are markedly collapsed, so that in this way we can explain what we have actually observed: a slowing up of absorption toward the end of the process.

It is understood, of course that gas absorption does not occur in the schematic way we have here depicted; actually, there is an incessant simultaneous exchange of all the gases involved. Bohr has shown that extremely small differences in partial pressures are sufficient to insure the diffusion of great amounts of gases through semipermeable membranes. Loewy and Luntz have shown that a difference of only a couple of millimeters of mercury suffices for the passage through the alveolar membrane of the 250 cc. of oxygen per hour per kilogram necessary basically for a man at rest.

We have seen that the anesthetic vapors and oxygen are rapidly absorbed.* It is now easy to understand how atelectasis might develop during the course of an operation as in the cases reported by H. Santee and Bergamini and Shepard. Should complete bronchial obstruction by viscid bronchial secretions occur during the course of an operation and the lung area involved contain a high percentage of anesthetic vapors and oxygen, atelectasis could readily be produced within an extremely short time.

A word should be said further about the rôle played by nitrogen in the gaseous exchanges in the lung. We have seen that it is one of the inert gases, requiring many hours for its absorption. Oxygen and carbon dioxide alone are absorbed by the lung in a few minutes; but when oxygen and carbon dioxide are considered in the atmospheric mixture their absorption periods are greatly prolonged the nitrogen of the air acting as a physical brake by virtue of its slow absorption into the blood. For this reason should bronchial obstruction occur, the time required for the production of atelectasis would be measured in hours rather than minutes. In this way the nitrogen of the air may be considered as a fortunate circumstance of Nature to delay alveolar gas absorption and production of atelectasis. This delay is valuable because it allows an interval

* The reader should refer to the two previous articles of this series.

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of time during which reaération of the lung could still be easily accomplished. Thus nitrogen may be thought of as the "safety brake," especially during anesthesia and the postoperative period, and may be considered as the "mechanical buffer" of the air.

From the foregoing paragraphs it is seen that in the absorption of anesthetic gases and vapors the nitrogen of the air allows their dilution and acts as a "brake," delaying their absorption. Without this gas general anesthesia by inhalation would not be possible.

Comment. There are three possible objections to our theory:

1. An equilibrium between the gases of the blood and alveolar blood could be reached after bronchial occlusion, and this should stop further exchange of gases.

2. Much more carbon dioxide should pass from the blood into the alveoli, because its speed of passage through the alveolar membrane is 30 times as great as for oxygen; thus atelectasis would be impossible.

3. The negative intrapleural pressure on the affected side in atelectasis has often been reported so increased that it was surmised that it should cause a passage of gases from the blood into the alveolus, and in this way prevent atelectasis.

The first objection can easily be answered. If all the gas molecules contained in the obstructed alveolus are absorbed this is due to the perfect elasticity of the alveolar membrane and to the great difference in diffusion speeds through it of oxygen, carbon dioxide and nitrogen. For these reasons a perfect equilibrium is never reached, and as Loewy and von Schroetter first showed, the exchange of gases is represented by an asymptotic curve.

The second objection is based on the great speed of passage of carbon dioxide through the alveolar membrane as compared with oxygen or nitrogen. We have already mentioned the experiment with the frog's lung demonstrating this point. Exner, using a soap film, showed that carbon dioxide would pass through it toward an indifferent gas with a speed of about 10 cc. per minute per square centimeter when under a pressure of only $\frac{1}{1000}$ of an atmosphere. But the rate of diffusion of gases is regulated by their partial pressures, so that, although carbon dioxide passes rapidly from the blood into the alveolus after bronchial obstruction an equilibrium is reached when its percentage becomes about 6 per cent of one atmosphere in the alveolus; after this point the actual mass of carbon dioxide exchanged through the respiratory membrane is small. In other words, the exchanges of carbon dioxide are rapidly accomplished, but the actual amount of carbon dioxide passing through the respiratory membrane is regulated exclusively by the differences in partial pressure of the gases respectively in the alveolar and venous air.

The third objection is of even greater importance. Habliston, in 1928, found the intrapleural pressure on the atelectatic side in

4 cases in man to be -12 , -13 , -16 and -25 mm. of mercury respectively, as against -4 , to -7 mm. on the unaffected side. Farris reported 2 similar cases in which relief was obtained by artificial pneumothorax. Wilson and Gordon (quoted by Habliston) and Ashbury have also reported such cases. Ashbury reported a case with a negative intrapleural pressure of -16 to -20 mm. of mercury; after inducing a partial pneumothorax on the affected side with 600 cc. of air the pressure became -4 to -7 mm. of mercury.

Presumably, with a negative intrapleural pressure of -16 to -20 mm. of mercury the intrapulmonary pressure is also -16 to -20 mm. of mercury below atmospheric pressure, for the gases in the lung are under a pressure which tends to be equal to the intrapleural pressure. In the case of a lung which is completely obstructed the pressure of gases within it tends to equal the intrapleural pressure because of the elasticity of the alveoli; thus, if the intrapleural pressure were -20 mm. of mercury the intrapulmonary pressure would also be about 20 mm. of mercury less than atmospheric, *i. e.*, about 740 mm. of mercury. If we consider the percentages of oxygen and carbon dioxide in the entrapped alveolar air as 5 and 6 per cent, of one atmosphere respectively, their partial pressures would be 38 and 45.6 mm. of mercury when the intrapulmonary pressure is 760 mm. of mercury and 37 and 44.4 mm. of mercury with an intrapulmonary pressure of 740 mm. Therefore, in the case under consideration the effect of a -20 mm. negative intrapleural pressure would be to lower the partial pressure of oxygen and carbon dioxide in the alveolus by only from 1 to 2 mm. However, it must also be remembered that the gases in the alveolar capillary blood are also subjected to corresponding diminution in their pressures, so that from a relative standpoint the partial pressures of the gases in the alveoli and in the alveolar capillaries have not changed. We may thus deduce that the increased negative intrapleural pressure does not materially influence the exchange of gases in the obstructed lung.

So far as the therapeutic effect of artificial pneumothorax is concerned, we agree with the foregoing authors quoted, as to its palliative effect by decreasing the displacement of the heart, but we completely disagree as to its efficacy in freeing the air passages of obstructing material. Pneumothorax cannot further compress a lung already atelectatic. Lastly, collapse of the lung by pneumothorax does not favor re-aeration or penetration of air into this lung; on the contrary, deeper respiration by producing dilatation of the bronchi is more apt to lead to the formation of airways between obstructing mucus and bronchial wall with subsequent expulsion of the obstacle to respiration.

Increased pressure of the entrapped air as produced in coughing or strained respiration would theoretically accelerate the absorp-

-13, -16 and -25 mm. of mercury 4, to -7 mm. on the unaffected side. cases in which relief was obtained by Wilson and Gordon (quoted by Hablis reported such cases. Ashbury reported a pleural pressure of -16 to -20 mm. a partial pneumothorax on the affected e pressure became -4 to -7 mm. of

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ffect of artificial pneumothorax is con- going authors quoted, as to its pallia- e displacement of the heart, but we e efficacy in freeing the air passages umothorax cannot further compress a stly, collapse of the lung by pneumo- on or penetration of air into this lung; ration by producing dilatation of the to the formation of airways between hial wall with subsequent expulsion

trapped air as produced in coughing theoretically accelerate the absorp-

tion of the alveolar gases, as has been maintained by van Allen and Adams. We think, however, that these authors have greatly exaggerated the importance of the factor, for an increase in intrapulmonary pressure in the obstructed lung can in these cases be produced only by an increase in the intrapulmonary pressure of the healthy lung. This means an increase in total intrathoracic pressure and consequently in the blood and blood gases as well. It seems that in these cases of van Allen and Adams, if atelectasis was produced earlier in animals incompletely anesthetized and struggling, this was due rather to excessive muscular work and exhaustion of oxygen in the blood, while at the same time rapid breathing washed out the carbon dioxid of the blood; the percentages of both gases and their partial pressures in the blood were decreased, causing a more rapid absorption of the entrapped air. We do not think, however, that from their data these authors were justified in coming to the conclusion that "narcotics are advisable because they aid in preventing atelectasis." The chief means the lung possesses to prevent atelectasis, or to overcome it once the bronchus is obstructed, is expulsion of the bronchial exudate by cough and deep breathing. Narcotics, on the contrary, deprive the lung of its best means of defense. We believe that for reasons previously described the more efficient treatment (both preventive and curative), besides rolling of the patient from side to side and encouraging him to breathe deeply, is hyperventilation by repeated inhalation of 10 per cent carbon dioxid in oxygen, (according to the method introduced by Henderson and Haggard in resuscitation after carbon monoxid poisoning), or bronchoscopic aspiration of bronchial exudate.

For a number of years we have endeavored to show that atelectasis is a well-defined clinical syndrome with a definite etiology, pathogenesis, pathology and treatment. It presents various clinical forms which can briefly be distinguished as follows:

1. According to the etiology: obstructive or compressive, post-operative or medical.
2. According to its distribution: multilobar (massive), lobar or lobular (patchy).
3. According to its duration: acute or chronic.
4. According to its evolution: simple or complicated.

The last variety comprises the cases in which infection follows because of the presence of the obstructing agent of microbes of more or less high virulence, so that an infectious process begins in the lung and is favored by the impaired drainage of the respiratory organ. Postoperative atelectasis in which Group 4 pneumococcus is always present represents a mild form of infection. Lobar pneumonia in which more virulent pneumococci are present represents another type of acute infectious atelectasis occurring as an accident in the course of pneumococcic bronchitis. Abscess and gangrene

of the lung are similarly infectious forms of septic bronchial obstruction and atelectasis, due to specific microorganisms, aërobes and anaërobes. The painstaking work of Smith, Allen, Joannides and others throws a new light on this last variety, justifying our conception.

We have also endeavored to prove that the pathologic process in the different forms of atelectasis develops along the same lines as in similar lesions in glandular organs, the ducts of which have been obstructed and to which the lung should be compared. We have shown that the circulation and the ventilation in lungs that have become atelectatic, from any cause, show exactly parallel changes, depending entirely on the condition of the pulmonary ventilation.

The present work, by showing the intimate mechanism of the production of apneumatosiis, can explain the pathogenesis of the different forms of the disease by sound physiologic principles. It shows, further, the importance of physiologic, physical and chemical consideration in the study of respiration in relation to thoracic surgery. Clinical and experimental evidence points to the conclusion that atelectasis is always due to complete bronchial obstruction. We wish to stress the great importance in the pathology of the lung of impairment of free bronchial drainage, and we believe that it has been demonstrated beyond doubt that atelectasis must be definitely associated with the idea of bronchial obstruction. The obstructing agent, whatever its nature, should be sought and treatment instituted for its removal and reaëration of the lung.

General Conclusions. 1. Experimental methods have been devised which give evidence that when a bronchus is completely obstructed the entrapped alveolar air rapidly undergoes qualitative and quantitative changes as determined by successive gas analyses.

2. Qualitatively, the percentages and partial pressures of the gases comprising the alveolar air tend to, but never quite, reach an equilibrium with the gases of the venous blood.

3. Quantitatively, the entrapped alveolar gases pass through the respiratory membrane into the blood circulating in the perialveolar capillaries until complete airlessness of the involved area is produced.

4. The mechanism of production of atelectasis in the compressed lung (pneumothorax, pleural exudate, intrathoracic tumors, etc.) is exactly the same as in bronchial obstruction.

5. Besides the gases of the air, diffusion of other gases was studied by introducing them into a lung previously rendered atelectatic. The different gases used in these experiments were: (a) Active gases, oxygen and carbon dioxide; (b) neutral gases, hydrogen, nitrogen and helium; (c) anesthetic gases or vapors, ether, ethyl chlorid, nitrous oxid and ethylene.

6. A new experimental method was devised which allows direct vision of the pulmonary changes occurring during the experiment.

fectious forms of septic bronchial obstruction to specific microorganisms, aërobes and anaerobes. The work of Smith, Allen, Joannides and others on this last variety, justifying our con-

clusion to prove that the pathologic process in atelectasis develops along the same lines as in other thoracic organs, the ducts of which have been compared. We have shown that the ventilation in lungs that have been collapsed and the ventilation in lungs that have not, show exactly parallel changes, thus confirming the condition of the pulmonary ventilation. Showing the intimate mechanism of the process, we can explain the pathogenesis of the disease by sound physiologic principles. It is the difference of physiologic, physical and chemical conditions of respiration in relation to thoracic conditions. Experimental evidence points to the conclusion that due to complete bronchial obstruction there is great importance in the pathology of atelectasis. Free bronchial drainage, and we believe that beyond doubt that atelectasis must be treated on the idea of bronchial obstruction. However its nature, should be sought and removed and re-aëration of the lung.

Experimental methods have been devised that when a bronchus is completely occluded, alveolar air rapidly undergoes qualitative changes determined by successive gas analyses. The partial pressures of the gases tend to, but never quite, reach an equilibrium with the venous blood.

Collapsed alveolar gases pass through the blood circulating in the perialveolar space. The uselessness of the involved area is proven by the action of atelectasis in the compressed lung, exudate, intrathoracic tumors, etc.) and bronchial obstruction.

The diffusion of other gases was studied in the lung previously rendered atelectatic. These experiments were: (a) Active gases, oxygen, carbon dioxide, hydrogen, nitro-
(b) neutral gases, hydrogen, nitrogen, carbon dioxide, ethyl chloride, ethyl ether, ethyl alcohol, etc.

A method was devised which allows direct measurements occurring during the experiment.

7. Nitrogen in the respiratory air plays the part of a "mechanical buffer," retarding the absorption of more diffusible and more soluble gases.

8. This experimental work has allowed the formation of a theory on the mechanism of atelectasis based on the physiology of exchange of gases in the lung.

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THE PATHOLOGY OF RHEUMATIC PNEUMONIA.

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THE pulmonary manifestations of rheumatic fever have been studied by many clinicians. Many years ago Fuller,¹ Cheadle,² Garrod³ and other English physicians wrote of "Rheumatic Pneumonias." It is probable that these earlier writers recognized clinically lesions similar to those which are the subject of this report. Some of their observations correspond very closely to what is today being identified as the clinical picture of rheumatic pneumonitis and rheumatic pleurisy. Garrod mentioned the transient character of the physical signs of the pulmonary lesions, but he stated that there is nothing peculiar in the postmortem appearance of such a lung or its pleura which would differentiate it from the ordinary acute inflammations.

Pulmonary lesions in the course of rheumatic fever are certainly not infrequent, as evidenced by the reports of Fuller,¹ Latham,⁴ Cheadle,² Garrod³ and in recent years by Thayer,⁵ Swift,⁶ Rabino- witz⁷ and Paul.⁸ They have been recognized rather commonly in the more severe cases of rheumatic fever studied by Dr. J. C. Small and ourselves at the Philadelphia General and Presbyterian Hospitals.

Until very recently, knowledge of the incidence and character of these changes has been based mostly on clinical observations. Pathologic study was inconclusive.

Among the lesions which others have described are: (1) Rheumatic fibrinous pleurisy; (2) rheumatic pleurisy with effusion; (3) atelectasis secondary to pleural effusion; (4) atelectasis secondary to

Effect of Lung Volume Reduction Surgery on Diaphragm Strength

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Since lung volume reduction surgery (LVRS) reduces end-expiratory lung volume, we hypothesized that it may improve diaphragm strength. We evaluated 37 patients for pulmonary rehabilitation and LVRS. Before and 8 wk after pulmonary rehabilitation, 24 patients had spirometry, lung volumes, diffusion capacity, incremental symptom limited maximum exercise test, 6-min walk test, maximal static inspiratory and expiratory mouth pressures, and transdiaphragmatic pressures during maximum static inspiratory efforts and bilateral supramaximal electrophrenic twitch stimulation measured. Twenty patients (including 7 patients who crossed over after completing pulmonary rehabilitation) had baseline measurements postrehabilitation, and 3 mo post-LVRS. Patients were 58 ± 8 yr of age, with severe COPD and hyperinflation (FEV_1 , 0.69 ± 0.21 L; RV, 4.7 ± 1.4 L). Nineteen patients had bilateral LVRS performed via median sternotomy and stapling, and 1 patient had unilateral LVRS via thorascopy with stapling. After rehabilitation, spirometry and D_{LCO}/V_A were not different, and lung volumes showed a slight worsening in hyperinflation. Gas exchange, 6-min walk distance, maximum oxygen uptake ($\dot{V}O_{2max}$), and breathing pattern during maximum exercise did not change after rehabilitation, but total exercise time was significantly longer. Inspiratory muscle strength ($P_{i_{max}}$, $P_{di_{max}}$ combined, $P_{di_{max}}$ sniff, $P_{di_{max}}$, $P_{di_{twitch}}$), was unchanged after rehabilitation. In contrast, after LVRS, FVC increased 21%, FEV_1 increased 34%, TLC decreased 13%, FRC decreased 23%, and $FRC_{trapped\ gas}$ and RV decreased by 57 and 28%, respectively. P_{CO_2} was lower (44 ± 6 versus 48 ± 6 mm Hg, $p < 0.003$) and 6-min walk distance increased (343 ± 79 versus 250 ± 89 m, $p < 0.001$), as did total exercise time during maximum exercise (9.2 ± 1.9 versus 6.9 ± 2.7 min, $p < 0.01$). Minute ventilation (29 ± 8 versus 21 ± 6 L/min, $p < 0.001$) and tidal volume (1.0 ± 0.33 versus 0.84 ± 0.25 L, $p < 0.001$) during maximum exercise increased whereas respiratory rate was lower (28 ± 6 versus 32 ± 7 breaths/min, $p < 0.02$). Measurements of respiratory muscle strength ($P_{i_{max}}$, 74 ± 28 versus 50 ± 18 cm H₂O, $p < 0.002$; $P_{di_{max}}$ combined, 80 ± 25 versus 56 ± 29 cm H₂O, $p < 0.01$; $P_{di_{max}}$ sniff, 71 ± 7 versus 46 ± 27 cm H₂O, $p < 0.01$; $P_{di_{twitch}}$, 15 ± 5 versus 7 ± 5 cm H₂O, $p < 0.01$) were all greater post-LVRS. Inspiratory muscle workload as measured by $P_{di\ T1}$ was lower following LVRS (0.07 ± 0.02 versus 0.09 ± 0.03 , $p < 0.03$). On multiple regression analysis, increases in $P_{i_{max}}$ correlated significantly with decreases in RV and $FRC_{trapped\ gas}$ after LVRS ($r = 0.67$, $p < 0.03$). We conclude that LVRS significantly improves diaphragm strength that is associated with a reduction in lung volumes and an improvement in exercise performance. Future studies are needed to determine the relationship and stability of these changes over time. Criner G, Cordova FC, Leyenson V, Roy B, Travaline J, Sudarshan S, O'Brien G, Kuzma AM, Furukawa S. Effect of lung volume reduction surgery on diaphragm strength.

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Lung volume reduction surgery (LVRS) has been advocated in select patients with severe, nonbullous, diffuse emphysema (1-7). Cooper and colleagues (1) reported the results of this surgery in 20 patients with severe chronic obstructive pulmonary disease (COPD) (mean FEV_1 , 0.77 L) and hyperinflation

(TLC, 8.5 L). These authors found that 6 mo after surgery mean FEV_1 increased by 82% (0.77 to 1.4 L), arterial PO_2 increased from 64 to 72 mm Hg, and 6-min walk distance increased by 33%. Other investigators have confirmed the beneficial effects of bilateral volume reduction (2) and, to a lesser extent, unilateral volume reduction (3-7), on improving spirometry and gas exchange, reducing residual volume, and enhancing exercise performance (8-11).

Several investigators have reported conflicting results on the effect of LVRS on respiratory muscle function (8-12). Although some have shown that LVRS increases diaphragm strength (12), and alters respiratory muscle recruitment during

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TABLE 1
INCLUSION AND EXCLUSION CRITERIA FOR LUNG VOLUME REDUCTION SURGERY

Inclusion criteria	
A.	New York Heart Association Class III–IV
B.	Evidence of airflow obstruction and hyperinflation by pulmonary function studies (i.e., FEV ₁ < 30% of predicted, postbronchodilator administration, FRC or TLC > 120% of predicted)
C.	Hyperinflation documented by chest X-ray and diffuse bullous emphysema documented by high-resolution CT scan
D.	Ventilation-perfusion mismatch documented in planned resected lung tissue by quantitative ventilation perfusion lung scan
Exclusion criteria	
A.	Patients with severe and refractory hypoxemia (PaO ₂ /Fio ₂ ratio < 150)
B.	Severe hypercapnic respiratory failure requiring mechanical ventilation
C.	The presence of significant cardiovascular disease
D.	The presence of severe pulmonary hypertension (mean pulmonary artery pressure > 50 mm Hg)
E.	Severe debilitated state with total body weight < 70% of ideal body weight
F.	Presence of significant extrapulmonary end organ dysfunction expected to limit survival
G.	Psychosocial dysfunction
H.	Continued smoking

Definition of abbreviation: CT = computed tomography.

exercise (10), others have shown no significant effect (11). Moreover, the effect of LVRS versus pulmonary rehabilitation on lung function, exercise capacity, or respiratory muscle strength has not been carefully delineated in any of these earlier reports (1–12).

Herein, we examine the effects of LVRS versus pulmonary rehabilitation on diaphragm strength in patients with severe, nonbullous diffuse emphysema.

METHODS

Patient Selection

Thirty-seven patients were evaluated for LVRS. Twenty-four patients underwent 8 wk of intensive outpatient pulmonary rehabilitation. A total of 20 patients, including seven of the previous 24 patients who underwent 8 wk of pulmonary rehabilitation, met LVRS criteria shown in Table 1. After being considered an acceptable candidate, patients had the protocol and LVRS explained to them in detail (Figure 1). The

study was approved by our Institutional Review Board for Human Research (Temple University School of Medicine, Philadelphia, PA).

Physiologic Measurements

Before and 8 wk after rehabilitation, 24 subjects performed a variety of pulmonary function studies (e.g., spirometry before and after bronchodilator administration, lung volumes measured by helium dilution and body plethysmography, diffusion capacity), incremental symptom-limited maximum exercise test, 6-min walk test, measurement of volitional maximum static inspiratory and expiratory mouth pressures, and transdiaphragmatic pressures measured during maximum static inspiratory efforts and during bilateral supramaximal twitch electrophrenic stimulation. Thirteen patients had similar physiologic measurements before and 3 mo after LVRS. In addition, seven patients had the preceding measurements made before and after 8 wk of outpatient pulmonary rehabilitation and then 3 mo post-LVRS.

Pulmonary function testing. Pulmonary function testing was performed (13) with a System 6200 Autobox DL plethysmograph (SensorMedics Corp., Yorba Linda, CA), using American Thoracic Soci-

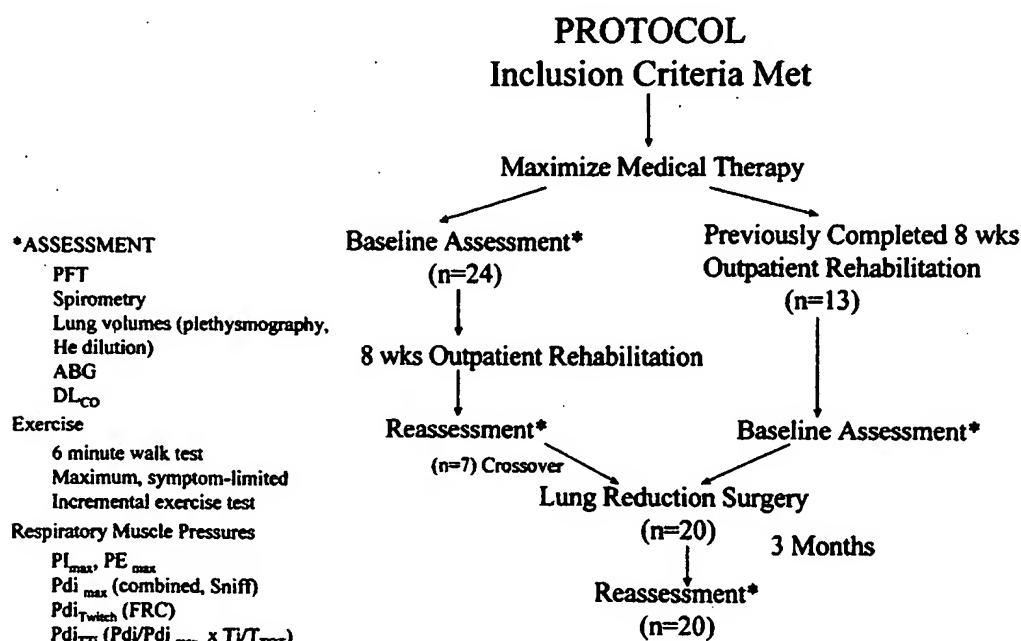


Figure 1. Outline of protocol for testing before and after pulmonary rehabilitation and lung volume reduction surgery.

TABLE 2
BASELINE CHARACTERISTICS OF ALL PATIENTS

Parameter	Value
Sex	F (23); M (14)
Age, yr	58 ± 8
Smoking, pack-years	59 ± 24
Prednisone use, %	39
Theophylline use, %	32
β-Agonist use, %	100
Anticholinergic use, %	92
O ₂ at rest, %	62
O ₂ during exercise, %	86
Albumin, mg/dl	4.0 ± 0.64
% IBW	119 ± 22

Definition of abbreviation: % IBW = percent ideal body weight.

ety guidelines. Vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and FEV₁/FVC were measured. Airway resistance (Raw) and thoracic gas volumes were measured in a body plethysmograph. Functional residual capacity (FRC) was also measured by helium dilution technique. FRC_{trapped gas} is the difference between FRC measurements made by body plethysmography and helium dilution.

Diffusion capacity for carbon monoxide (DL_{CO}) was measured by the single-breath technique. It is reported as the carbon monoxide-diffusing capacity per unit of alveolar volume (DL_{CO}/VA).

Maximum voluntary ventilation (MVV) was measured with the subjects seated upright and instructed to breathe maximally in a deep and rapid manner for a sustained period of 12 s. At least two trials were performed, with the highest value reported.

All data reported are postbronchodilator results presented in absolute numbers and as a percentage of normal predicted values (14).

Exercise testing. Patients underwent incremental, maximal treadmill exercise (Precor, 9.4 sp; Precor, Bothell, WA) starting at 0% incline and 1 mph. Incline increased by 3% and speed by 1.5 mph every 3 min until symptom-limited maximum. Oxygen uptake (V_{O₂}), carbon dioxide production (V_{CO₂}), minute ventilation (V_E), tidal volume (V_T), and respiratory rate (f_R) were also recorded by a metabolic cart (SensorMedics 2900). Transcutaneous oxygen saturation (Nellcor N-200, Nellcor, Chula Vista, CA) and multiple-lead EKG (ECG Horizon; SensorMedics) were continuously recorded. Patients requiring oxygen with exercise used the same level of inspired oxygen at each exercise evaluation. At each exercise test conclusion, dyspnea was rated using a visual analog scale from 0 (no breathlessness) to 10 (severe breathlessness) (15). On a different day, a walk distance test was measured, with subjects encouraged to ambulate in a 100-ft corridor their maximum distance in 6 min (16).

Respiratory muscle pressures. Mouth pressures were measured using a previously reported technique (17). P_{i,max} was measured from functional residual capacity (FRC), whereas P_{es,max} was measured near

TABLE 3
BASELINE PHYSIOLOGIC DATA

Parameter	Value
Number of patients, n	37
FVC, L (% predicted)	2.4 ± 0.7 (69 ± 14)
FEV ₁ , L (% predicted)	0.69 ± 0.21 (28 ± 8.3)
TLC, L (% predicted)	7.1 ± 1.7 (136 ± 17)
RV, L (% predicted)	4.7 ± 1.4 (246 ± 57)
DL _{CO} /VA, min/mm Hg	2.2 ± 0.64 (57 ± 16)
PaO ₂ /F _{IO₂}	322 ± 59
6 MWD, m	274 ± 106
V _{O₂} max, ml/kg/min	12.4 ± 3.2 (48 ± 14)
V _E max, L/min	25.5 ± 8.6

Definition of abbreviations: FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; TLC = total lung capacity; RV = residual volume; DL_{CO}/VA = diffusion capacity/alveolar volume; 6 MWD = 6-min walk distance; V_{O₂}max = maximum oxygen consumption during symptom-limited exercise test; V_Emax = maximum minute ventilation during symptom-limited exercise test.

total lung capacity (TLC). Tests were repeated until at least three attempts varied less than 5%, the average of three tests were then reported.

Transdiaphragmatic pressure measurement. Following topical anesthesia (4% lidocaine), two thin-walled balloon-tipped catheters were placed via the nares, one into the lower esophagus (esophageal pressure, P_{es}) and the other into the stomach (gastric pressure, P_{ga}) (18). Both catheters were connected to pressure transducers (range, ± 100 cm H₂O; Validyne, Northridge, CA). Transdiaphragmatic pressure (P_{di}) was displayed as the electronic subtraction of P_{es} from P_{ga}. A plaster cast was then placed over the anterior abdomen to minimize outward displacement of the abdominal wall during electrophrenic stimulation. Voluntary P_{di} was measured against an occluded airway using a combined expulsive-Mueller maneuver (P_{di,max combined}) during visual oscilloscopic feedback with subjects seated upright in a high-backed chair (19). In addition, maximum transdiaphragmatic pressures were measured during a maximum sniff maneuver (P_{di,max sniff}) (20) and uncoached maximum inspiratory effort (P_{di,max}). The average of three values of P_{di,max} during each separate maneuver, all within 5% of each other, are reported.

Electrophrenic stimulation. Compound diaphragm action potentials (CDAPs) were measured bilaterally by a pair of 3-mm EMG surface electrodes placed 2 mm apart in the seventh intercostal space in the anterior axillary line. The site for optimum phrenic nerve stimulation was located by using anatomic landmarks (21). Stimulus voltage was incrementally increased until there was no further increase in CDAP amplitude. Once maximum stimulus voltage was achieved, it was further increased by 20% to ensure supramaximal diaphragm activation.

A modified neck brace housing the right and left phrenic nerve stimulus probes was used to ensure consistency in phrenic nerve stimulation. The phrenic nerves were stimulated transcutaneously (S88 stimulator; Grass, Quincy, MA) with 100–140 V (approximately 30 mA), 0.1 ms in duration, to produce diaphragm twitch pressures (P_{di,twitch}). There was an approximately 20 to 30 min interval between the end of maximum voluntary static maneuvers and the onset of P_{di,twitch} testing.

P_{di,twitch} at FRC. With the subject seated with upright posture, bilateral phrenic nerve stimulation was delivered at functional residual capacity (FRC) after closure of an in-line three-way valve at end expiration. P_{es} was continuously monitored to ensure that end-expiratory lung volume had returned to a consistent baseline before valve closure. Six to 15 consecutive twitches (each twitch separated by at least a 3-s pause) were delivered at FRC. Twitches analyzed were those considered acceptable after ensuring that the FRC was at baseline and twitch morphology was consistent. Three values, all within 5%, were averaged and reported as P_{di,twitch}.

Surgical Technique

Lung resections were performed via median sternotomy and bilateral stapling (n = 19 patients) or unilateral thoracoscopy with stapling (1 patient). The goal for resection was to remove 20–40% of the volume of each lung, guided by the visual judgment of the same surgeon. High-resolution computed tomography of the chest and quantitative ventilation-perfusion scans were used preoperatively to target resection of lung regions with the worst emphysema, poorest perfusion, and greatest gas trapping.

Pulmonary Rehabilitation

Pulmonary rehabilitation consisted of twenty-four 2-h sessions over an 8-wk period. Rehabilitation included education, physical and respiratory care instruction; psychosocial support; and supervised exercise training by an exercise physiologist. After baseline exercise tests, all subjects received an individualized exercise prescription based on symptom-limited maximum. Patients used a motor-driven treadmill, performed arm cycling, and lifted arm and leg weights under supervision. The intensity of the program was increased on an individual basis.

Data Analysis

All data are expressed as mean ± SD except where otherwise noted. Student paired two-tailed *t* tests were used to compare data before and after rehabilitation and before and after LVRS. Stepwise and multiple linear regressions were used to evaluate changes associated

TABLE 4
SPIROMETRY AND LUNG VOLUMES BEFORE AND AFTER
8 wk OF PULMONARY REHABILITATION

	Baseline (n = 24)		8 Weeks Postrehabilitation (n = 24)		p Value
	Actual	Percentage Predicted	Actual	Percentage Predicted	
Spirometry					
FVC, L	2.43 ± 0.68	71 ± 13	2.45 ± 0.64	73 ± 15	0.72
FEV ₁ , L	0.74 ± 0.2	30 ± 7.2	0.75 ± 0.2	30 ± 7.6	0.53
FEV ₁ /FVC	0.31 ± 0.04		0.30 ± 0.03		0.55
Body plethysmography					
TLC, L	6.8 ± 1.2	134 ± 16	7.1 ± 1.4	138 ± 18	0.05
RV, L	4.3 ± 0.9	231 ± 37	4.6 ± 1.2	240 ± 52	0.09
FRC, L	5.4 ± 1.0	180 ± 31	5.4 ± 1.3	182 ± 30	0.92
FRC, L (helium dilution)*	4.5 ± 1.2	157 ± 39	4.2 ± 1.0	145 ± 31	0.04
FRC _{trapped gas} [†] , L	0.9 ± 0.9		1.2 ± 1.1		0.06
MVV, L	31 ± 10		33 ± 11		0.10
D _{LCO} /VA, min/mm Hg	2.3 ± 0.6	59 ± 17	2.3 ± 0.8	60 ± 20	0.4
Raw, [‡] cm H ₂ O/L/s	5.8 ± 2.3	404 ± 127	4.9 ± 1.5	344 ± 88	0.03

Definition of abbreviations: FRC = functional residual capacity; MVV = maximum voluntary ventilation; Raw = airway resistance; FRC_{trapped gas} = difference between FRC measured by body plethysmography and helium dilution techniques.

* n = 22.

† n = 20.

‡ n = 18.

with increases in diaphragm strength. All statistical analyses were conducted using a commercially available computer software program (Sigmapstat, version 2.0; Jandel, San Rafael, CA). p Value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Baseline demographic characteristics are shown in Table 2. Baseline physiologic data are shown in Table 3. All subjects had severe airflow obstruction (FEV₁, 0.69 ± 0.21 L), hyperinflation, and air trapping (TLC, 7.1 ± 1.7 L; RV, 4.7 ± 1.4 L), and decreased exercise performance (V̇O_{2max} 12.4 ± 3.2 ml/kg/min).

Physiologic Data before and after 8 wk of Pulmonary Rehabilitation

Spirometry and lung volumes. Table 4 shows spirometry, lung volumes, and diffusing capacity before and 8 wk after rehabili-

tation in 24 subjects. FVC, FEV₁, and FEV₁/FVC were not different before and after rehabilitation, TLC, RV, FRC_{trapped gas}, and FRC were either slightly increased or unchanged after rehabilitation. Raw was significantly decreased but D_{LCO}/VA remained unchanged.

Gas exchange and exercise performance. Table 5 shows gas exchange and cardiopulmonary exercise studies before and after rehabilitation. Oxygenation and Pco₂ were not different following rehabilitation. V̇O_{2max}, V̇E_{max}, V̇T_{max}, and maximum respiratory rate were also not different postrehabilitation during maximum exercise. Total exercise time was greater postrehabilitation (6.9 ± 1.7 versus 5.9 ± 1.6 min, p < 0.002), but the 6-min walk distance was unchanged.

Respiratory muscle strength. Table 6 shows maximum mouth and transdiaphragmatic pressures, and Pdi_{twitch} before and after pulmonary rehabilitation. Respiratory muscle function did not change following rehabilitation. Pdi_{max}, Pdi_{twitch}, P_i_{max}, Pdi_{max sniff}, Pdi_{max combined}, P_E_{max}, and Pdi T_{ti} were similar before and after rehabilitation.

TABLE 5
GAS EXCHANGE AND EXERCISE PERFORMANCE AT BASELINE
AND AFTER 8 wk OF PULMONARY REHABILITATION

	Baseline (n = 22)	8 Weeks Postrehabilitation (n = 22)	p Value
Gas exchange			
PaO ₂ /F _i O ₂	331 ± 58	328 ± 66	0.78
PaCO ₂ , mm Hg	45 ± 6	45 ± 7	0.87
6 MWD,* m	293 ± 105	300 ± 111	0.57
Symptom-limited maximal treadmill exercise[†]			
Total exercise time, min	5.9 ± 1.6	6.9 ± 1.7	0.002
V̇O _{2max} , ml/kg/min	13.1 ± 3.2	12.9 ± 2.8	0.6
V̇E _{max} , L/min	28 ± 9	27 ± 8	0.31
V̇T _{max} , L	0.9 ± 0.29	0.9 ± 0.30	0.37
f _{breath} , breaths/min	36 ± 9	36 ± 7	0.81

Definition of abbreviations: V̇T_{max} = maximum tidal volume; f_{breath} = maximum breathing frequency.

* n = 24.

† n = 23.

TABLE 6
MOUTH AND TRANSDIAPHRAGMATIC PRESSURES BEFORE
AND AFTER 8 wk OF PULMONARY REHABILITATION

	Baseline (n = 22)	Postrehabilitation (n = 22)	p Value
P _i _{max} , cm H ₂ O	48 ± 21	53 ± 23	0.17
P _E _{max} , cm H ₂ O	89 ± 33	93 ± 35	0.11
Pdi _{max combined} ,* cm H ₂ O	67 ± 33	71 ± 41	0.5
Pdi _{max sniff} , [†] cm H ₂ O	63 ± 29	68 ± 30	0.33
Pdi _{max} , cm H ₂ O	56 ± 27	62 ± 38	0.18
Pdi _{twitch} , [‡] cm H ₂ O	11 ± 5	12 ± 7	0.65
Pdi T _{ti} [†]	0.1 ± 0.05	0.08 ± 0.04	0.35

Definition of abbreviations: P_i_{max} = maximum inspired mouth pressure; P_E_{max} = maximum expired mouth pressure; Pdi_{max combined} = maximum transdiaphragmatic pressure during combined expulsive-Mueller maneuver; Pdi_{max sniff} = transdiaphragmatic pressure during maximum sniff; Pdi_{max} = transdiaphragmatic pressure during maximum uncoached inspiratory effort; Pdi_{twitch} = transdiaphragmatic pressure during twitch stimulation; Pdi T_{ti} = Pdi/Pdi_{max} × T_i/T_{tot}.

* n = 16.

† n = 20.

‡ n = 17.

TABLE 7
SPIROMETRY AND LUNG VOLUMES BEFORE AND 3 mo POST-LVRS

	Before (n = 20)		3 mo Post-LVRS (n = 20)		p Value
	Actual	Percentage Predicted	Actual	Percentage Predicted	
Spirometry					
FVC, L	2.4 ± 0.77	67 ± 17	2.9 ± 0.67	80 ± 16	0.001
FEV ₁ , L	0.64 ± 0.19	26 ± 9	0.86 ± 0.2	36 ± 10	0.001
FEV ₁ /FVC	0.31 ± 0.11		0.30 ± 0.07		0.8
Body plethysmography					
TLC, L	7.5 ± 1.9	138 ± 21	6.5 ± 1.4	120 ± 20	0.001
RV, L	5.0 ± 1.7	257 ± 70	3.6 ± 1.1	189 ± 59	0.001
FRC, L	6.0 ± 1.6	193 ± 30	4.6 ± 1.3	150 ± 30	0.001
FRC, L (helium dilution)*	4.4 ± 1.3	140 ± 34	3.8 ± 1.2	124 ± 30	0.001
FRC _{trapped gas} * L	1.56 ± 1.0		0.66 ± 0.66		0.001
MVV, L	26 ± 9		35 ± 4		0.001
D _{lCO} /V _A , min/mm Hg	2.1 ± 0.59	55 ± 16	2.3 ± 0.52	59 ± 14	0.19
Raw, cm H ₂ O/L/s	7.3 ± 2.7	543 ± 222	4.8 ± 1.6	356 ± 127	0.001

For definition of abbreviations, see Table 4.

* n = 19.

Physiologic Data before and after LVRS

Spirometry and lung volume. Table 7 shows spirometry, lung volumes, and diffusing capacity before and 3 mo after LVRS in all 20 subjects. Before surgery, subjects were severely obstructed and moderately to severely hyperinflated. Three months following LVRS, FVC increased 21%, FEV₁ increased 34%, TLC decreased 13%, FRC decreased 23%, and FRC_{trapped gas} and residual volume decreased by 57 and 28%, respectively. Raw also decreased 34% postoperatively.

Gas exchange and exercise performance. Table 8 shows gas exchange and cardiopulmonary exercise studies before and after LVRS in all patients. Postoperatively, there were no significant changes in oxygenation; however, carbon dioxide tensions were lower (44 ± 6 versus 48 ± 6 mm Hg, p < 0.003). After LVRS, 6-min walk distance (343 ± 79 versus 250 ± 89 m, p < 0.001), total exercise time (9.2 ± 1.9 versus 6.9 ± 2.7 min, p < 0.001) and V_{O₂max} (15.7 ± 4 versus 11.5 ± 3 ml/kg/min, p < 0.001) all significantly increased. Following surgery, minute ventilation (29 ± 8 versus 21 ± 6 L/min, p < 0.001) during maximum exercise was greater, and was associated with a higher tidal volume (1.0 ± 0.33 versus 0.84 ± 0.25 L, p < 0.001) and lower respiratory rate (28 ± 6 versus 32 ± 7 breaths/min, p < 0.02) at peak exercise.

TABLE 8
GAS EXCHANGE AND EXERCISE PERFORMANCE
BEFORE AND 3 mo POST-LVRS

	8 wk (n = 20)	3 mo Post-LVRS (n = 20)	p Value
Gas exchange			
PaO ₂ /F _I O ₂	313 ± 65	322 ± 40	0.46
PaCO ₂ , mm Hg	48 ± 6	44 ± 6	0.003
6 MWD, m	250 ± 89	343 ± 79	0.001
Symptom-limited maximal treadmill exercise*			
Total exercise time, min	6.9 ± 2.7	9.2 ± 1.9	0.008
V _{O₂max} , ml/kg/min	11.5 ± 3	15.7 ± 4	0.001
V _E max, L/min	21 ± 6	29 ± 8	0.001
V _T max, L	0.84 ± 0.25	1.0 ± 0.33	0.001
f _{breath} max, breaths/min	32 ± 7	28 ± 6	0.02

For definition of abbreviations, see Table 5.

* n = 15.

Respiratory muscle strength. Table 9 shows maximum mouth and transdiaphragmatic pressures, and Pdi_{twitch} before and after LVRS. Following surgery, P_imax, Pdi_{max} combined, Pdi_{max} sniff, Pdi_{max}, and Pdi_{twitch} were all greater. P_Emax was not different. Tension time index for the diaphragm (Pdi/Pdi_{max} × T_i/T_{tot}), however, was lower.

Body weight. In 20 patients who underwent LVRS, there was no significant difference in body weight before and after surgery (148 ± 23 versus 151 ± 24% IBW, p < 0.31).

Determinants of Increases in Diaphragm Strength Post-LVRS

In single regression analysis, increases in Pdi_{max} combined, Pdi_{max}, and Pdi_{max} sniff were not found to correlate with the reductions in FRC (r = 0.16, p = 0.57), RV (r = 0.22, p = 0.44), RV/TLC (r = 0.29, p = 0.28), FRC_{trapped gas} (r = 0.26, p = 0.35), or reductions in PaCO₂ (r = 0.04, p = 0.88). Similarly, no correlation was found with these parameters and the measured increases in Pdi_{sniff}, Pdi_{twitch}, and P_imax (Table 10).

Stepwise multiple regression found that postoperative reductions in RV and FRC_{trapped gas} were strong determinants of the postoperative increases in P_imax (r = 0.67, p < 0.03). However, RV and trapped gas at FRC were not predictive of postoperative increases in Pdi_{max} (r = 0.33, p = 0.49), Pdi_{twitch} (r = 0.44, p = 0.47), and Pdi_{max} sniff (r = 0.42, p = 0.38).

TABLE 9
MOUTH AND TRANSDIAPHRAGMATIC PRESSURES
BEFORE AND 3 mo POST-LVRS

	Baseline (n = 16)	3 mo Post-LVRS (n = 16)	p Value
P _i max, cm H ₂ O	50 ± 18	74 ± 28	0.002
P _E max, cm H ₂ O	80 ± 31	86 ± 38	0.39
Pdi _{max} combined, cm H ₂ O	56 ± 29	80 ± 25	0.007
Pdi _{max} sniff, cm H ₂ O	46 ± 27	71 ± 17	0.007
Pdi _{max} , cm H ₂ O	51 ± 23	78 ± 30	0.001
Pdi _{twitch} , cm H ₂ O	6.7 ± 5	15 ± 5	0.007
Pdi TTI [†]	0.09 ± 0.03	0.07 ± 0.02	0.03

For definition of abbreviations, see Table 6.

* n = 13.

† n = 14.

‡ n = 11.

TABLE 10
CORRELATIONS BETWEEN CHANGES IN TRANSDIAPHRAGMATIC PRESSURES, LUNG VOLUMES, P_{aCO_2} , AND PERCENT IDEAL BODY WEIGHT AFTER LVRS

	$P_{di_{max}}$		$P_{di_{sniff}}$		$P_{di_{twitch}}$		$P_{i_{max}}$	
	r	p	r	p	r	p	r	p
FRC, L	0.16	0.57	0.17	0.56	0.23	0.49	0.22	0.42
RV, L	0.21	0.44	0.25	0.39	0.05	0.87	0.44	0.086
RV/TLC	0.29	0.28	0.31	0.27	0.04	0.90	0.135	0.62
$FRC_{trapped\ gas}$, L	0.26	0.35	0.38	0.20	0.39	0.27	0.42	0.12
P_{aCO_2} , mm Hg	0.04	0.88	0.12	0.68	0.006	0.98	0.08	0.77
% IBW	0.01	0.97	0.01	0.96	0.20	0.57	0.30	0.26

* Multiple linear regression using RV and trapped gas as dependent variables and $P_{i_{max}}$ as independent variable showed $r = 0.67$ and $p = 0.03$.

DISCUSSION

Our data confirm that LVRS in patients with severe non-bullous diffuse emphysema improves spirometry and exercise tolerance and reduces lung volume (1-12). Moreover, our data show that LVRS improves diaphragm strength, lowers inspiratory muscle workload during ventilation, and affords emphysema patients a more comfortable breathing pattern (less rapid and shallow) during maximum exercise. These data clearly demonstrate that LVRS improves diaphragm, lung, and airway mechanics, in contrast to pulmonary rehabilitation alone.

The adverse effects of hyperinflation on diaphragm mechanics have been reported by others (22-29). These effects include diaphragm precontraction length foreshortening (22-25), reduced radius of diaphragm curvature (23), impaired diaphragm blood flow (26), decreased diaphragm insertional rib cage action (27), increased internal elastic load (22), and a decrease in the area of apposition of the costal diaphragm with the chest wall (28, 29). As a result, hyperinflation reduces the diaphragm force-generating capacity and limits the ability of the patient with COPD to tolerate increased ventilatory workloads during exercise, or when complicating medical conditions occur. A treatment modality such as LVRS, that simultaneously decreases ventilatory workload and improves respiratory pump action, has the combined advantage of diminishing ventilatory workload while simultaneously improving maximum breathing capacity.

Several studies have reported the effects of LVRS on respiratory muscle recruitment during exercise and on inspiratory muscle strength. Bloch and coworkers (10) found in 19 patients with severe emphysema, who underwent bilateral or unilateral LVRS, that abdominal paradoxical motion monitored by respiratory inductive plethysmography decreased significantly during restful breathing post-LVRS. Benditt and colleagues (9) examined breathing pattern and respiratory muscle recruitment before and after LVRS by examining changes in pleural and gastric pressures. Following LVRS, they found a reduction in end-expiratory esophageal and gastric pressures at rest, and at isoexercise observed a rightward shift in the slope of the esophageal versus gastric pressure plot, suggesting increased use of the diaphragm. Although both studies suggested an improvement in diaphragm strength was responsible for the changes in breathing pattern post-LVRS, no measurements were reported.

Studies examining the effects of LVRS on respiratory muscle strength have reported conflicting results. Teschler and colleagues (12) reported the effects of LVRS on inspiratory muscle strength in 17 severely obstructed and hyperinflated patients with COPD (FEV_1 , 0.82 ± 0.07 L; RV, $337 \pm 31\%$). Twelve of the 17 patients had unilateral LVRS. The in-

vestigators found that mean $P_{i_{max}}$ increased by 52% and mean $P_{di_{max\ sniff}}$ increased by 28%, 1 mo postoperatively. In contrast, Martinez and co-workers (8) measured maximum mouth and transdiaphragmatic pressures in 17 subjects before and after bilateral LVRS. They found a 21% increase in $P_{i_{max}}$ after LVRS, but no significant change in $P_{di_{max\ sniff}}$. Keller and colleagues (11) found no effect of unilateral LVRS on $P_{i_{max}}$ in 25 subjects despite significant changes in spirometry, lung volume, 6-min walk test, and ventilatory function during maximum exercise testing.

Why LVRS has shown conflicting results on respiratory muscle strength in the preceding reports is unclear. Several explanations could include the small numbers of patients studied, variability in the techniques used to measure respiratory muscle strength, the effect that rehabilitation may have had on patient well-being and muscle strength, and the effect of studying respiratory and exercise mechanics at different time points post-LVRS.

Our study used a variety of techniques in measuring transdiaphragmatic pressure (both volitional and nonvolitional techniques) and found highly significant increases in maximum mouth and transdiaphragmatic pressures post-LVRS. Moreover, in contrast to earlier investigations, we are confident that these changes were not due to other factors, such as pulmonary rehabilitation, adjustments in medications, or other medical interventions. Patients who received pulmonary rehabilitation in our study (the control group) showed no improvements in maximum mouth or transdiaphragmatic pressures despite comparable medical care by the same clinicians.

Although it has been hypothesized that LVRS improves diaphragm function by reducing end-expiratory lung volume, we failed to demonstrate correlations between changes in transdiaphragmatic pressures and reductions in lung volume. Increases in $P_{i_{max}}$ post-LVRS tended to correlate with reductions in residual volume ($r = 0.44$, $p = 0.08$) and multiple linear regression with RV, $FRC_{trapped\ gas}$ and $P_{i_{max}}$ showed significance ($r = 0.67$ and $p = 0.03$). It is unclear why $P_{i_{max}}$ showed a correlation with a reduction in RV while transdiaphragmatic pressure did not. The larger number of subjects studied with $P_{i_{max}}$, and the lesser degree of variability in its measurement than in measurements of transdiaphragmatic pressure between subjects, may be potential factors.

Besides a reduction in lung volume, other factors, such as electrolyte abnormalities, or a learning effect in the performance of repeated respiratory tasks, could have been partially responsible for the improvements in diaphragm strength that we found post-LVRS. However, none of our patients had electrolyte imbalances before or after surgery and our control group of rehabilitation patients performed a similar number of repeated ventilatory tasks.

In addition to a reduction in end-expiratory lung volume, a decrease in the arterial partial pressure for carbon dioxide, an increase in body weight, and a change in thoracoabdominal configuration postoperatively all could have been important factors contributing to increases in diaphragm strength. Hypercapnia has been reported to affect diaphragm contractility adversely (30). Autopsy studies have shown that a reduction in body weight is associated with a significant loss in diaphragm mass, thickness, and area (31), and these changes have been shown to decrease maximum respiratory pressures and reduce respiratory reserve (32). In our study, patient body weight did not change post-LVRS. The fact that $P_{E_{max}}$ was not increased after LVRS suggests that systemic factors, such as electrolyte changes or a reduction in hypercapnia, did not substantially affect global measurements of respiratory muscle strength.

A significant reduction in corticosteroid use postoperatively also could have had a beneficial impact on diaphragm strength. Several human (33) and animal (34) studies have shown the detrimental effects of steroids on diaphragm structure and function. Whether the reduction in postoperative steroid use accounts for some of the increase in diaphragm strength that we observed postoperatively is unclear from our results and cannot be discounted.

One limitation to our study is that diaphragm strength was measured only 3 mo after surgery, a time at which maximum postoperative changes in diaphragm length may not yet have occurred. Similowski and colleagues (35) have shown that adaptive changes may occur in the diaphragm in chronically hyperinflated patients with COPD. In eight well-nourished, chronically hyperinflated, but stable patients with COPD (FEV_1 , 1.06 ± 0.4 L; TLC, 7.85 ± 1.13 L [mean \pm SD]), they demonstrated that while Pdi_{twitch} at FRC was lower than that found in normal control subjects, at increased comparable lung volumes (TLC), patients with COPD tended to have greater Pdi_{twitch} values.

In our study, measurement of diaphragm strength at one time point (3 mo postoperatively) may not have reflected final diaphragm muscle adaptation to its new precontraction length. We may have underestimated the effects of lung reduction surgery on increasing diaphragm force generation if the diaphragm is still operating on the ascending limb of the length-tension curve and undergoing further lengthening. It is hoped that future studies will evaluate the effects of surgical reductions in lung volume on diaphragm force generation in sequential fashion, so as to determine the maximum effects of acute lung reductions on diaphragm force generation.

Patients receiving comprehensive outpatient pulmonary rehabilitation in our study failed to show any significant changes in lung function, as has been previously reported by others. Similar to a large prospective, randomized controlled trial conducted by Ries and colleagues (36), we found significant increases in treadmill endurance time during maximum exercise testing. However, the increase in endurance we report is much less than that reported by Ries and coworkers, whose patients were less obstructed and hyperinflated (FEV_1 , 1.21 ± 0.55 L, RV/TLC, 60%) suggesting that their patients were able to tolerate more intensive rehabilitation that resulted in greater improvements.

In summary, LVRS results in significant improvements in spirometry, exercise performance, and diaphragm strength in patients with severe, diffuse, nonbullous emphysema and hyperinflation. Future studies are needed to confirm our results and to determine the long-term stability of these favorable changes over time.

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Re-expansion of Refractory Atelectasis Using a Bronchofiberscope with a Balloon Cuff*

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For the re-expansion of refractory atelectasis, it is necessary to remove sputum in the airway and to deliver the intrabronchial positive pressure to the atelectatic lobe in order to overcome the critical opening pressure of the alveoli. Selective intrabronchial air insufflation is effective for this purpose, because with this procedure, endobronchial pressure in the atelectatic region can be selectively increased without elevation of the pleural surface pressure in the

surrounding region of the lung. The inflator devised consisted of a flexible bronchofiberscope with a small balloon cuff at the distal end; through the fiberscope air was insufflated into the atelectatic lung. Using our procedure, we successfully performed intrabronchial insufflation in 14 of 15 patients with atelectasis, who had failed to respond to conventional therapy. In six patients, atelectasis recurred, and the same treatment was successfully performed again.

Treatment of atelectasis that occurs after surgery or trauma has considerably improved since the introduction of bronchofiberscopic procedures at the bedside. Despite the improvement, refractory atelectasis that is difficult to re-expand is sometimes seen. For the treatment of these cases, various devices, such as a rigid bronchoscope with a cuff,¹ have been developed. We also have devised a bronchofiberscope with a cuff,² and using this instrument, we found that selective positive pressure ventilation to the airway in the atelectatic region resulted in easy and controlled re-expansion of refractory atelectasis.

INSTRUMENTS AND METHODS

The bronchofiberscope (Olympus B3R) was used, and a rubber

balloon cuff (2.0 cm in length, 0.5 cm in diameter) was devised and attached to the end (Fig 1). The balloon cuff was similar to that used in tracheal tube for anesthesia but was smaller with a thin rubber membrane. The cuff was connected to a tube (1 mm in diameter, 50 cm in length) which was used to inject air into the cuff. For attaching the cuff to the bronchofiberscope, short cuff forceps were used (Fig 2).

The intubation of the bronchofiberscope into the airway was performed after spraying 2 percent lidocaine solution into the pharynx or trachea. The bronchofiberscope was directly inserted into the trachea with a mouthpiece while the patient was in the supine or sitting position.

After the bronchofiberscope was inserted into the trachea, the fiberscope was advanced into the bronchus while aspirating sputum in the airway. Then the balloon cuff was expanded with air injection until it was in contact with bronchial wall. Air was insufflated into the peripheral airway by an Ambu bag or anesthesia instruments through the biopsy channel of the bronchofiberscope. Positive pressure was exerted into the peripheral airway. During insufflation, dilatation of the bronchial lumen was observed endoscopically. When necessary, suction of the sputum and the positive pressure ventilation was performed alternatively. This procedure assures the

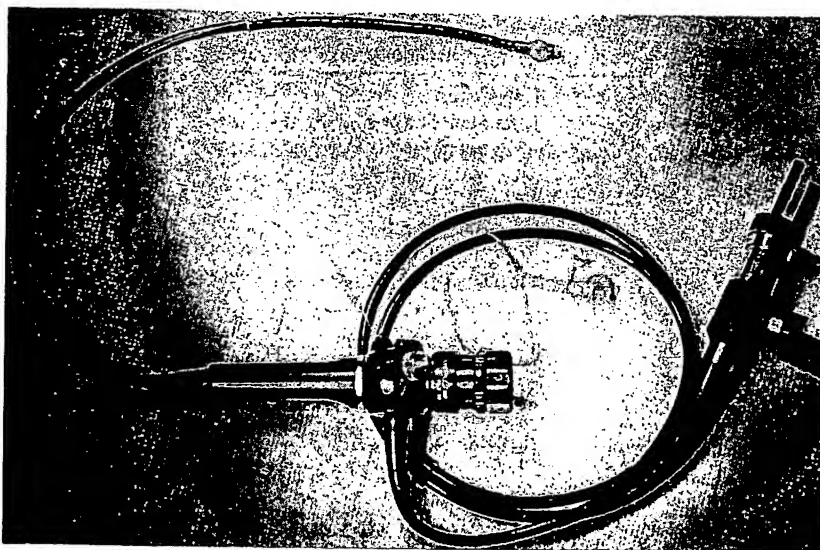


FIGURE 1. Flexible bronchofiberscope with a balloon cuff. The cuff is placed at the distal end of the fiberscope and is expanded by air injection through a long, thin tube connected with the cuff.

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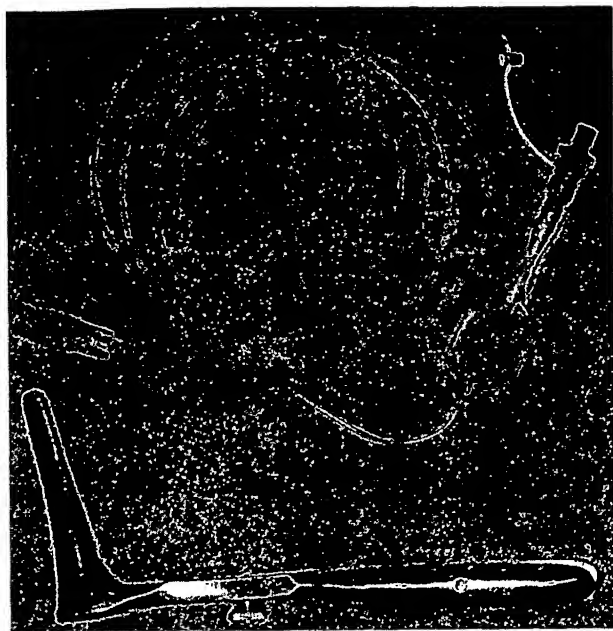


FIGURE 2. A balloon cuff and a small forceps used for attaching the cuff to bronchofiberscope.

expansion of the peripheral lung. It is recommended that the pressure be exerted while monitoring the expansion of the lung by x-ray fluoroscopy. In many cases, the lung expanded with only a little resistance and ventilation.

RESULTS

Clinical Effects

Table 1 shows 15 patients who were successfully treated by selective intrabronchial positive pressure ventilation.

In six of these patients, atelectasis had continued for five or more days, and in two patients, pulmonary collapse was found just after the contralateral thoracotomy; the onset of atelectasis was unclear in two patients.

The primary disorder complicated with atelectasis included those of the central nervous system, trauma to the chest and abdomen, and surgical procedures. In these patients, expectoration was often difficult and a large amount of sputum was present in the airway. In all cases, the atelectatic lesions readily expanded except for case 10. However, recurrence was seen within several days after the treatment in six patients, including four with central nervous system disorders, one with serious trauma, and in one patient following operation for esophageal cancer. The lungs of these patients re-expanded completely by the reapplication of the present method.

Figure 3 shows a typical case. The patient (No. 7 in Table 1) had considerable pain due to abdominal contusion and pelvis fracture, and difficulty in coughing and expectorating sputum. Atelectasis in the left lung was found six days after surgery for the trauma, and intrabronchial suction and regional positive pressure ventilation were undertaken, after which the atelectatic area expanded sufficiently, but the condition recurred after two days. Though suction of sputum was performed bronchoscopically, the lung did not re-expand sufficiently (Fig 3A). After selective positive pressure ventilation was exerted by insufflating air into the left main bronchus, the lung re-expanded completely (Fig 3B).

DISCUSSION

To re-expand the collapsed alveoli, the transpulmonary pressure must be greater than the critical opening pressure of alveoli. When atelectasis occurs in large areas of the lung, such as unilateral total lung atelectasis, pleural surface pressure becomes markedly negative pressure, causing the alveoli to expand.^{3,4} In such cases, transpulmonary pressure in the atelectatic alveoli can easily increase over critical opening pres-

Table 1—Patients Treated with Selective Intrabronchial Air Insufflation

Case No.	Age/Sex	Atelect Site*	Duration	Primary Disease	Effect
1	54/M	rLL	8 Days	L flail chest	Healed
2	70/M	lLL	30 Days	L spontaneous pneumothorax	Healed
3	28/M	rUL	Immediate after operation	After operation for L pneumothorax	Healed
4	44/M	lLL	1 Day	After gastrectomy	Healed
5	61/M	lLL	1 Day	After operation for abdominal wall hernia	Healed
6	72/M	l total	3 Days	Cervical contusion	Recurrent
7	65/M	l total	4 Days	Abdominal contusion pelvis fracture	Recurrent
8	58/M	rML	10 Days	Middle lobe syndrome	Healed
9	59/F	l total	5 Days	Cerebral apoplexy	Recurrent
10	56/M	l total	20 Days	Cervical contusion	Failed
11	82/M	r total	2 Days	Cerebral infarct	Recurrent
12	63/F	rML	Unclear	Middle lobe syndrome	Healed
13	65/F	rLL	5 Days	After operation for esophageal cancer	Recurrent
14	11/M	l total	Immediate after operation	Intrabronchial foreign body	Healed
15	66/M	rML	Unclear	Middle lobe syndrome	Healed

*rLL, right lower lobe; lLL, left lower lobe; rUL, right upper lobe; rML, right middle lobe; recurrent, healed after the recurrent; and, failed, atelectasis remained.

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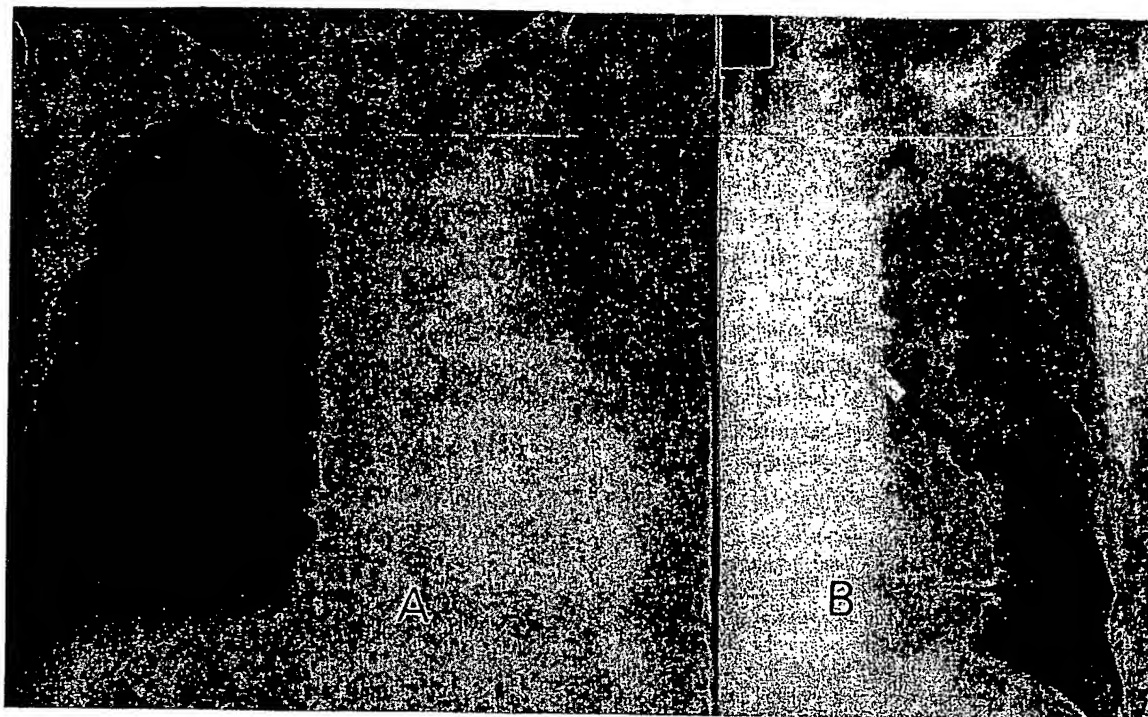


FIGURE 3. Chest roentgenogram of case 7. A (left): Recurrent atelectasis in left lung re-expanded insufficiently with suction of sputum using bronchofiberscope. B (right): Selective intrabronchial positive pressure ventilation was applied using the bronchofiberscope with cuff, resulting in complete expansion of the atelectatic lung.

sure, and the atelectatic lung may more easily expand than that in small areas of the lung. However, some cases with refractory atelectasis do not expand after suction of sputum. These cases have both low lung compliance and a high critical opening pressure which, if left untreated, may result in chronic atelectasis.

When air has been blown into the trachea through the endotracheal tube, the insufflated air is more easily distributed into the normal area of the lung than the atelectatic region which has high airway resistance and low lung compliance, resulting in the compression of atelectatic region from surfaces of the surrounding lungs. Then, often observed by fluoroscopic roentgenograms or surgery, the atelectatic lung hardly re-expands by the positive pressure ventilation through the endotracheal tube under about 20 cm H_2O airway pressure.

In contrast, the air selectively insufflated into the bronchus involved with atelectasis, acts to effectively open the obstructed airway in the atelectatic lung, while the surrounding lung² is scarcely affected.

In 1974, Sachdeva⁵ reported treatment of two patients with atelectasis using an endotracheal tube with a cuff. Bowen et al¹ reported immediate re-expansion of atelectatic lungs in 15 patients after exerting positive pressure using a rigid bronchoscope with a cuff at the distal end.

Since a fiberoptic bronchoscope is flexible and can be inserted into the segmental bronchi, the method of using a bronchofiberscope with a cuff is excellent for

exerting selective positive pressure into a lobe or a segment of lung. As the present method is easily applicable to insertion into the trachea, it has the advantage that intubation can be performed under topical anesthesia of the airway at bedside.

Because the present method permits the efficient delivery of positive pressure, attention should be paid to the possibility of rupturing the alveoli and pleural membrane by overinflation. Fortunately, we have not encountered such a case to date. For protection against barotrauma, we exerted the positive pressure while observing the extent of lung expansion by x-ray fluoroscopy.

Experimentally, positive pressure has been exerted in the lungs of adult dogs through the trachea after thoracotomy. The results showed no damage to the lungs at pressures under 30 cm H_2O ; however, rupture and bleeding of the alveoli were observed under 60 cm H_2O .⁶

Another problem is the recurrence of atelectasis after the treatment. From our experience, recurrence of atelectasis often appeared in patients with central nervous system disorders, after operation for esophageal cancer, and in patients with persistent atelectasis. Thus, in the postoperative treatment of these patients, bronchofiberscopy or tracheostomy must often be performed to keep in the inflated lung after the procedure.

Miki⁷ reported alveolar collapse persisting in large areas of the lung after re-expansion of the atelectasis

continuing for three months in adult dogs. We also have surgically treated the cases with lung atelectasis persisting for several months caused by a foreign body and trauma in the left main bronchus. It was necessary to perform bronchofiberscopic air insufflation several times after bronchoplastic surgeries.

The present results demonstrate that our method was effectively applicable to cases with acute atelectasis provoked by obstruction of the airway with sputum, which could not be readily re-expanded by conventional methods. For prolonged atelectasis or that associated with disorders of the nervous system, supplementary treatment is often required in addition to the present method. Moreover, care should be taken in exerting positive pressure to atelectasis in lungs with emphysematous changes.

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Comparison of Short-term Functional Outcomes Following Unilateral and Bilateral Lung Volume Reduction Surgery*

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Harold I. Palevsky, MD, FCCP; John Hansen-Flaschen, MD, FCCP;
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Study objectives: To compare short-term functional outcomes following unilateral and bilateral lung volume reduction surgery (LVRS) performed in patients with advanced emphysema.

Methods: LVRS was performed unilaterally in 32 patients and bilaterally in 119 patients. Pulmonary function testing and 6-min walk test (6MWT) were performed preoperatively and repeated at 3 to 6 months postoperatively.

Results: Bilateral LVRS was associated with increased in-hospital mortality (10% vs 0%, $p < 0.05$) and a higher incidence of postoperative respiratory failure (12.6% vs 0%; $p < 0.05$) compared with unilateral LVRS. There was no significant difference in duration of air leaks between unilateral and bilateral groups, but the mean hospital stay was significantly longer following bilateral LVRS (21.1 ± 32.0 days vs 14.2 ± 14.0 days; $p < 0.05$). Preoperatively, there was no significant difference between the unilateral and bilateral groups with respect to FEV₁, FVC, residual volume, or 6MWT distance. However, for all of these parameters, the magnitude of improvement was significantly greater following bilateral LVRS. Notably, the magnitude of improvement in each parameter following unilateral LVRS exceeded half that following bilateral LVRS, suggesting that functional outcomes after the unilateral procedure were disproportionate to the amount of tissue resected. Serial functional assessment of seven patients undergoing staged unilateral procedures (two unilateral procedures separated in time by at least 3 months) demonstrated somewhat unpredictable responses; failure to achieve a favorable response to the initial procedure did not necessarily portend a similar outcome with the contralateral side, and vice versa.

Conclusions: Bilateral LVRS produces a greater magnitude of short-term functional improvement than does the unilateral procedure and should be considered the procedure of choice for most patients. Unilateral LVRS should be reserved for patients in whom factors contraindicating entrance into one hemithorax exist.

(CHEST 1998; 113:890-95)

Key words: emphysema; lung volume reduction surgery; video-assisted thoracic surgery

Abbreviations: LVRS=lung volume reduction surgery; MS=median sternotomy; NS=not significant; RV=residual volume; 6MWT=6-min walk test; VATS=video-assisted thoracoscopic surgery

Lung volume reduction surgery (LVRS) has recently emerged as a promising palliative surgical option for selected patients with advanced, disabling emphysema. Studies performed at multiple centers

have documented improvement in pulmonary function, exercise tolerance, gas exchange, dyspnea, and quality of life following LVRS in some but not all patients.¹

The surgical technique of LVRS has evolved over time. As originally developed by Brantigan et al² in the 1950s, LVRS was performed in unilateral fashion via a posterolateral thoracotomy incision, with serial wedge resections taken from the most diseased areas of lung, and manual suturing of the resected surface.² This procedure was plagued by protracted air leaks and by a mortality rate approximating 20%, likely related in part to inability of this tenuous population to tolerate the adverse impact of the

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thoracotomy incision on lung function. More than three decades later, Wakabayashi et al³ revisited the notion of volume reduction by introducing a technique of unilateral thoracoscopic laser ablation of small, diffuse bullae in the emphysematous lung. In 1995, Cooper et al⁴ returned to the original concept of Brantigan et al of surgical resection, modifying the technique by employing a median sternotomy to permit a bilateral procedure, and utilizing a linear stapler overlaid with bovine pericardium to simultaneously resect, staple, and buttress the lung. More recently, both unilateral and bilateral stapled resection have been performed via thoracoscopic technique.⁵⁻⁸ To date, the optimal surgical approach has yet to be defined.

Distinct and evolving surgical preferences of the thoracic surgeons at our institution have afforded us the opportunity to scrutinize the outcomes associated with these various technical approaches. We have demonstrated previously that bilateral stapled resection performed by either median sternotomy (MS) or thoracoscopic technique results in similar functional improvement.⁹ This current study compares short-term functional outcomes achieved with unilateral LVRS with those following bilateral surgery.

MATERIALS AND METHODS

Patient Population

Between September 1993 and April 1996, 151 patients with severe emphysema underwent LVRS at the University of Pennsylvania Medical Center. Patients who underwent bullectomy for giant bullous disease were not included in this population.

One hundred nineteen patients underwent bilateral LVRS (88 by MS and 31 by video-assisted thoracoscopic surgery [VATS]) and 32 underwent unilateral procedures (2 by MS and 30 by VATS). The decision to perform unilateral LVRS was predicated on one of two factors. In eight patients, unilateral LVRS was performed because of features in the contralateral lung that contraindicated a bilateral procedure (prior thoracic surgery or pleurodesis, uniformly and severely diseased lung). In 24 patients, a unilateral VATS operation was chosen as the initial procedure of a planned staged approach, with intent to perform contralateral "completion" LVRS 3 months subsequently. This approach reflected in part the conservative surgical philosophy that characterized the early phases of our program. Ten of the patients in the unilateral group went on to have contralateral LVRS. In the remaining 14 patients, contralateral LVRS was not pursued for the following reasons: patient declined due to satisfaction with outcome from unilateral LVRS (10 patients); poor outcome with subsequent listing for lung transplantation (3 patients); and intercurrent abdominal surgery for bowel perforation (1 patient). In the later stages of our LVRS program, the bilateral procedure, performed simultaneously by either MS or VATS, became the preferred procedure in the absence of contraindicating factors.

Patients selected to undergo surgery had evidence of severe airflow obstruction with an FEV₁ in the approximate range of 20

to 30% of predicted, were severely hyperinflated with a residual volume (RV) measured by body plethysmography in excess of 200% of predicted, and had heterogeneously distributed disease with large zones of hypoventilated and hypoperfused lung documented by quantitative ventilation/perfusion lung scanning. Exclusion criteria were as follows: (1) PCO₂ >50 mm Hg; (2) pulmonary artery systolic pressure >50 mm Hg (measured by Doppler echocardiography or right heart catheterization); (3) active or recent (within 3 months) cigarette smoking; (4) body weight under or exceeding 20% of predicted ideal range; (5) significant bronchospasm with wide fluctuations in FEV₁; (6) copious daily sputum production; and (7) poor functional status (see below). During the screening process, approximately 60% of referred patients were excluded from surgery.

Those patients preliminarily deemed to be suitable candidates for surgery were required to enroll in a formal outpatient pulmonary rehabilitation program for 6 weeks. A 6-min walk test (6MWT) was then performed and only those patients capable of walking in excess of 600 feet were permitted to undergo surgery. Patients unable to meet this minimum acceptable performance criterion were encouraged to complete an additional 6 weeks of rehabilitation, after which they were again reassessed with a 6MWT. Those patients with a persistently poor functional status despite rehabilitation were subsequently excluded.

During the preoperative evaluation, conventional medical therapy utilizing inhaled and systemic bronchodilators was maximized. An attempt was made to wean oral corticosteroids to the lowest dose capable of maintaining stable lung function; patients whose daily steroid requirements exceeded 20 mg of prednisone or its equivalent were excluded.

Functional Evaluation

Pulmonary function testing, including spirometry and measurement of lung volumes, was performed preoperatively and again 3 to 6 months postoperatively using standard techniques. Body plethysmography was uniformly employed to measure lung volumes, as it provides a more accurate assessment of lung volumes than does helium dilution in this population of patients with severe airflow obstruction. Arterial blood gas samples were drawn on all patients as part of the preoperative evaluation. Since many patients could not tolerate breathing room air, the arterial blood gas samples were frequently drawn with the patient breathing supplemental oxygen, making comparisons of PO₂ meaningless. However, the main purpose of the blood gas determinations was to exclude patients with significant hypercapnia (PCO₂>50 mm Hg).

Exercise tolerance was assessed with a standard 6MWT. Patients performed the test in a wide, straight hallway after receiving pretest instructions; they were not coached during the study. Supplemental oxygen was titrated throughout the test to maintain a minimum arterial oxyhemoglobin saturation of 90%. The preoperative 6MWT was performed after a minimum of 6 weeks of outpatient pulmonary rehabilitation. The postoperative 6MWT measurements were obtained 3 to 6 months following surgery; during this period, the patients completed an additional 6 weeks of pulmonary rehabilitation.

Operative Technique and Postoperative Care

Surgical reduction of lung volume was achieved in a uniform fashion through the performance of serial nonsegmental wedge resections employing a linear stapling device as previously described.^{4,9} The most diseased portions of lung, as assessed by preoperative ventilation/perfusion scanning and direct intraoperative inspection, were targeted for resection. Staple lines were

buttressed with strips of bovine pericardium as previously described.¹⁰ An attempt was made to reduce the overall volume of the lung by 20 to 30% based on visual inspection. At the completion of the procedure, two chest tubes were placed in each operated-on hemithorax. In our initial experience, chest tubes were placed to -20 cm wall suction. In later cases, water seal was immediately utilized, if tolerated, in an attempt to avoid disruption of the fresh suture line.

All patients were extubated at the end of the procedure. Immediate postoperative analgesia was provided by means of a continuous epidural infusion of morphine or fentanyl; bupivacaine was concurrently employed in selected cases. After the first several postoperative days, an attempt was made to convert the patient to intermittent oral opioid analgesia. Vigorous chest physiotherapy was employed throughout the postoperative period. Early ambulation was encouraged and a low-level supervised exercise program consisting of hallway walking and stationary bicycling was initiated once the patient was ambulatory. Chest tubes were pulled within 24 h of documented cessation of air leaks.

Postoperatively, patients were required to re-enroll in an outpatient pulmonary rehabilitation program for an additional 6 weeks.

Statistical Analysis

Data are expressed as mean \pm SD. Unpaired Student's *t* test was utilized to compare differences in continuous variables between the unilateral and bilateral LVRS groups. In addition to comparing group mean FEV₁, FVC, RV, and 6MWT data at baseline and postoperatively, the incremental change in each parameter following surgery was calculated as the mean of the individual incremental changes for each patient. Chest tube duration and length of stay differences were analyzed using the Mann-Whitney *U* test. Fisher's Exact Test was employed to compare differences in categorical variables.

A *p* value of <0.05 was considered statistically significant.

RESULTS

Postoperative Course

Thirty-two patients underwent a total of 42 unilateral procedures (10 patients had a contralateral procedure performed subsequent to the first). There were no operative deaths (*ie*, within 30 days) associated with any of these procedures and all patients were successfully discharged to home. Six operative deaths (5%) occurred among the 119 patients undergoing bilateral LVRS. An additional six patients in the bilateral LVRS group died prior to discharge home, including two patients transferred to long-term ventilator facilities who died 5 and 8 months after surgery, respectively. Thus, cumulative in-hospital mortality for the bilateral LVRS group was 10% compared with zero for the unilateral group (*p*<0.05).

All patients in both groups were extubated within 12 h of surgery. None of the patients undergoing unilateral procedures required reintubation at any time during their hospital course. In contrast, 15

patients (12.6%) undergoing bilateral procedures required reintubation for varying periods of time (*p*<0.05).

Mean chest tube duration (reflecting duration of air leaks) was 13.6 ± 14.3 days for the unilateral group and 14.9 ± 16.8 days for the bilateral group (*p*=not significant [NS]). Mean length of stay was 14.2 ± 14.0 days and 21.1 ± 32.0 days for the unilateral and bilateral groups, respectively (*p*<0.05).

Functional Outcomes

Paired preoperative and 3- to 6-month postoperative functional data were available for 23 of 32 (72%) patients in the unilateral group and 86 of 119 (72%) patients in the bilateral group. The effect of LVRS on conventional pulmonary function parameters is shown in Table 1. There was no difference in baseline FEV₁, FVC, or RV between the groups. Postoperatively, both groups demonstrated significant improvement in all parameters. However, the incremental change in FEV₁, FVC, and RV was significantly greater following the bilateral procedure. Specifically, the mean increase in FEV₁ was 0.25 ± 0.31 L vs 0.16 ± 0.22 L (*p*<0.001) following bilateral and unilateral LVRS, respectively. For FVC, the incremental increase was 0.42 ± 0.64 L following bilateral LVRS and 0.34 ± 0.71 L after unilateral LVRS (*p*<0.001). Finally, RV decreased by an average of 1.38 ± 1.33 L in the bilateral group and by 0.90 ± 0.75 L in the unilateral group (*p*<0.001), suggesting that the bilateral procedure more effectively reduced the degree of hyperinflation.

The impact of surgery on exercise performance, as assessed by measurement of 6MWT distance, is shown in Table 2. Preoperatively, 6MWT distance was approximately 10% lower in the unilateral group, possibly reflecting a surgical bias to utilize this procedure in more "tenuous" patients, but the difference was not statistically significant. Although

Table 1—Effect of LVRS on Pulmonary Function*

	Unilateral (n=23)	Bilateral (n=86)	<i>p</i> Value
FEV ₁ , pre, L	0.67 ± 0.26	0.74 ± 0.24	NS
FEV ₁ , post, L	0.83 ± 0.36	0.99 ± 0.40	<0.05
Δ FEV ₁ , L	0.16 ± 0.22	0.25 ± 0.31	<0.001
FVC, pre, L	2.18 ± 0.86	2.26 ± 0.72	NS
FVC, post, L	2.51 ± 0.89	2.68 ± 0.82	NS
Δ FVC, L	0.34 ± 0.71	0.42 ± 0.64	<0.001
RV, pre, L	5.18 ± 1.60	5.02 ± 1.29	NS
RV, post, L	4.44 ± 1.14	3.61 ± 1.04	0.05
Δ RV, L	-0.90 ± 0.75	-1.38 ± 1.33	<0.001

*Pre=preoperative; post=postoperative.

Table 2—Effect of LVRS on 6MWT*

	Unilateral (n=23)	Bilateral (n=86)	p Value
6MWT, pre, feet	912±311	1,026±284	NS
6MWT, post, feet	1,054±314	1,201±330	0.05
Δ6MWT, feet	147±326	195±251	<0.001

*See Table 1 footnote (and text) for explanation of abbreviations.

both groups realized significant improvement in walk distance following surgery, the magnitude of improvement was greater in association with the bilateral procedure (195±251 feet vs 147±326 feet; $p<0.001$).

For each functional parameter, we calculated the ratio of the mean incremental change following unilateral LVRS to that following bilateral LVRS (Fig 1). This ratio ($\Delta U/\Delta B$) was 0.64 for FEV₁, 0.81 for FVC, 0.65 for RV, and 0.75 for 6MWT. Thus, for all functional parameters, the unilateral procedure resulted in a functional improvement exceeding half that achieved with the bilateral procedure.

Impact of Sequential Unilateral Procedures

Ten patients underwent sequential unilateral procedures separated in time by 3 months; complete follow-up data following each procedure were available for seven patients. Shown in Table 3 is the magnitude of change in FEV₁ measured 3 months following each of the two procedures. Notably, the contribution of each unilateral procedure to the net improvement in FEV₁ was highly variable. Only one

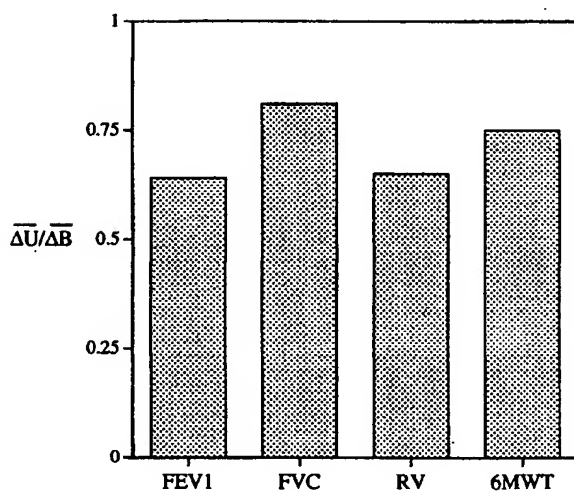


FIGURE 1. Ratio of the mean incremental change following unilateral LVRS to that following bilateral LVRS. This ratio ($\Delta U/\Delta B$) was calculated for each of the measured functional parameters (FEV₁, FVC, RV, and 6MWT distance).

Table 3—Impact of Sequential Unilateral Procedures on FEV₁

Patient	ΔFEV ₁ , mL		Net
	Side 1	Side 2	
1	+250	+280	+530
2	+420	-30	+390
3	+50	+230	+280
4	-180	+460	+280
5	+140	+60	+200
6	+180	-50	+130
7	+130	-10	+120

patient realized marked incremental increases following both procedures while several others responded favorably to only one of the two procedures. Failure to achieve a favorable response to the initial procedure did not necessarily portend a similar outcome with the subsequent one, and vice versa.

DISCUSSION

Multiple series published to date document outcomes exclusively following unilateral^{3,5-9,11} or bilateral LVRS.^{4,9} Attempts to compare these two procedures across different institutions are confounded by interinstitutional variations in patient selection criteria, requirements for pulmonary rehabilitation, and postoperative care. Further complicating comparisons are differences in surgical technique among the centers. Although the bilateral procedures were typically performed with stapled resection of tissue, unilateral LVRS at a number of centers was performed by means of laser ablation, a technique likely inferior to the stapled approach.¹² Our single-center comparison of unilateral and bilateral LVRS ensures greater uniformity in these variables, including the exclusive use of stapled resection for both unilateral and bilateral procedures.

We have demonstrated that both unilateral and bilateral stapled LVRS result in short-term improvement in pulmonary function and exercise tolerance. However, the magnitude of improvement in all parameters examined was greater following the bilateral procedure. Nevertheless, it must be acknowledged that the added functional benefits of the bilateral procedure were accompanied by a significantly longer hospital length of stay and greater rates of postoperative respiratory failure and in-hospital mortality. As we have reported previously,⁹ the deaths that occurred following bilateral LVRS occurred almost exclusively in association with the median sternotomy approach. Indeed, in the current series, in-hospital mortality was only 3% for the

subset of patients undergoing bilateral LVRS by VATS technique compared with almost 13% for those undergoing the median sternotomy approach. Since functional outcomes following the two bilateral techniques are identical,⁹ these observations suggest that the bilateral VATS approach is functionally superior to the unilateral procedure yet essentially equivalent in risk.

Curiously, the degree of improvement in pulmonary function and walk distance achieved with the unilateral procedure was greater than half that following bilateral LVRS. Specifically, the incremental changes in FEV₁ and RV following the unilateral procedure approximated two thirds that of the bilateral, while the incremental improvement in FVC and 6MWT distance was roughly three quarters that of bilateral LVRS. Since a conscious attempt to resect more than the standard volume of lung tissue was not made, it is unlikely that excessive removal of tissue following the unilateral procedure accounted for the observed effect. Rather, we speculate that the seemingly disproportionate benefit of unilateral resection may relate to the capacity of this procedure to influence diaphragmatic configuration bilaterally. For obvious reasons, the diaphragm ipsilateral to the operated-on lung ascends following the unilateral procedure. As a result of ipsilateral shift of the mediastinum, we have observed radiographically the ascension of the contralateral hemidiaphragm as well. Martinez et al¹³ have recently confirmed that the beneficial effects of LVRS relate in part to enhancement of diaphragmatic function, as evidenced by improvement in parameters of respiratory muscle strength.

Our study is not the first single-center comparison but corroborates and expands on similar experiences reported by McKenna et al¹⁴ and Cooper et al.¹⁵ Both groups reported superior physiologic outcomes following the bilateral stapled approach, including a greater likelihood of achieving freedom from supplemental oxygen. Unlike these previous reports, our study is the first (to our knowledge) to examine the physiologic impact of sequentially performed unilateral procedures. Performance of two unilateral LVRS procedures in a staged fashion has been suggested as a strategy to be utilized in more tenuous patients and, indeed, represented a preferred approach in the early phase of our own program. We have shown in the present study, however, that results utilizing this strategy are highly unpredictable. All of the seven patients described in our series demonstrated net improvement in the FEV₁ after completion of the two procedures, ranging from 0.12 to 0.53 L. Notably, however, the contributions of each unilateral procedure to the net improvement were highly variable. Only one patient manifested

marked incremental improvement in the FEV₁ following each of the two procedures. In four patients, improvement in FEV₁ occurred predominantly following the initial procedure and in two patients the converse was true.

In addition to the unpredictable responses, staged LVRS is associated with an increase in cumulative hospital days compared with simultaneously performed bilateral LVRS.⁹ Further undermining the role of staged LVRS is the observation that bilateral LVRS can be safely performed even in patients with severely impaired lung function. In our series, of 19 bilateral LVRS procedures performed in patients with an FEV₁ \leq 0.5 L, only two in-hospital deaths occurred. Although no deaths occurred following nine unilateral procedures in a comparable group, the difference in observed mortality rates was not statistically significant. McKenna et al¹⁴ similarly observed that operative mortality following unilateral and bilateral LVRS in severely compromised patients (FEV₁ < 0.5 L; age \geq 75 years; or PO₂ \leq 50 mm Hg) was comparable. In light of the unpredictable benefits of the staged procedure, the increased hospital stay, and the ability to perform bilateral LVRS safely even in marginal candidates, there does not appear to be a clear-cut role for the use of staged LVRS.

Several shortcomings of this study must be acknowledged. The study was retrospective in nature and patients were not assigned to a particular procedure in random fashion. It is possible that patients perceived to be more "tenuous" were assigned to the unilateral procedure based on the surgical bias that it would be a "gentler" and better tolerated procedure. The fact that the mean preoperative 6MWT distance for the unilateral group was approximately 10% less than that of the bilateral group supports this contention, but this difference was not statistically significant. Furthermore, no significant differences in baseline pulmonary function parameters were detected, suggesting that the two groups were reasonably well matched with respect to degree of pulmonary impairment.

The unilateral and bilateral groups did not evolve contemporaneously, as six unilateral procedures were performed before the first bilateral procedure occurred and the bilateral procedure, unless contraindicated, supplanted the unilateral approach in the latter stages of the program. This disproportionately subjected the unilateral group to a possible "learning curve" phenomenon, making it even more impressive that morbidity and mortality in this group was negligible. Protocols for candidate selection and preoperative and postoperative care were standardized throughout the years of the study, with the exception that chest tube management shifted from routine use of wall suction to immediate use of water

seal beginning in mid-1995. This change affected an equal proportion of patients from each group (38% of unilateral and 44% of bilateral procedures were performed after this change). Thus, we do not believe that differences in perioperative care had a significant influence on the results observed in the two groups.

Paired preoperative and postoperative functional assessment was incomplete, available on approximately 70% of patients in each group. The fact that an equal proportion of patients in each group were unavailable for follow-up mitigates to some degree the potential impact of this problem. Nevertheless, incomplete follow-up likely biases the data in favor of more optimal outcomes, as those with poor outcomes are likely to be less willing to return.

Finally, we chose to focus exclusively on physiologic outcome parameters and did not scrutinize subjective responses to the procedure or other secondary outcomes measures. Such measures would have shed additional light on whether the observed differences in functional outcomes influenced aspects of disease of particular relevance to the patient's daily existence such as the degree of dyspnea or the need for continued utilization of oxygen. However, we believe that the parameters we chose as primary outcomes measures are of paramount importance in assessing the impact of this procedure on the principal functional derangements associated with COPD, *ie*, airflow obstruction, hyperinflation, and exercise limitation.

In conclusion, we have found that bilateral LVRS produces short-term functional outcomes that are superior to those of the unilateral procedure. This comes at the expense of increased postoperative morbidity and mortality, although in our hands, these adverse events can be minimized through use of thoracoscopic rather than MS technique in the performance of bilateral LVRS. Based on its superior short-term functional outcomes and acceptable risk profile, we favor bilateral LVRS as the procedure of choice. Because unilateral LVRS does appear to be of some benefit and is extremely safe, it should be considered as an acceptable alternative for patients in whom one lung is deemed unsuitable because of prior thoracic surgery, pleurodesis, or uniformly

diseased tissue. These observations must be considered as preliminary and in need of corroboration by randomized, prospective trials involving a longer period of observation.

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NEVER-ENDING TASK:

Clearing the Airways

by Janet C. Sclafani, RRT, RPFT

Clearing airways is dependent on the application of several different modalities. Methodologies include directed cough, chest physical therapy, autogenic drainage, the use of mucolytics, and adequate hydration.

The cough is an important mechanism to clear secretions from the airway. The cough begins with the stimulation of a receptor. Nerve endings within the epithelium of the airway become irritated and trigger the reflex of cough. Cough effectiveness is dependent on the patient eliciting high gas flows and velocity throughout the airways. The expiratory flow velocity during the cough determines the effectiveness of each effort. For the cough to effectively remove secretions, the secretions must be moved into the path of the expiratory gas flow.

During a cough, the airways vibrate, creating the movement of secretions in the adjacent airways and promoting clearance. Factors that affect the cough effort include inspiratory and expiratory muscle weakness. While inspiratory muscle weakness limits the volume of inhaled gas, weakness of the expiratory muscles will generate low expiratory pressure. At low lung volumes, both the elastic recoil of the lung and the length of the expiratory muscles are reduced. Both of these factors decrease expiratory pressure during cough.

Respiratory muscles can be trained for strength and endurance. Some modalities include isometric training, inspiratory muscle training, and incentive spirometry.

Directed cough

An effective cough effort can be accomplished with training. Voluntary control over the reflex can be achieved by increasing glottic control as well as inspiratory and expiratory muscle strength. The "huffing" technique of coughing (forced expiratory technique, or FET) is perhaps the best method for those with weak inspiratory and expiratory muscles. One to three huffs are elicited at mid to low lung volumes with the glottis open. This is followed by controlled diaphragmatic pursed-lip breathing. The process is repeated until secretions are loosened and expectorated.

Most patients can also apply self-compression of the chest wall by using a brisk adduction movement of the upper extremities, that is, extending

the arms forward during the expiratory phase of the cough maneuver. The caregiver may also apply external compression of the thorax during the forced exhalation.

The directed cough technique is usually not contraindicated except in cases of elevated intracranial pressure and reduced coronary artery perfusion. Potential for aspiration, presence of abdominal pathologies, untreated bleeding disorders, and pneumothorax should be considered and assessed by the practitioner. Mechanical compression of the thorax is contraindicated in the presence of osteoporosis and flail chest.

Complications to directed cough include reduced coronary artery perfusion and increased

bral perfusion, incontinence, headache, and fatigue. Pneumothorax, rib fracture, chest pain, and vomiting are also known complications. The patient should be monitored for pain, discomfort, and adverse neurological and cardiac function. The outcome of the cough effort is assessed by the volume of the secretions produced, improvement in breath sounds, and the patient's own assessment and response to the therapy.

Directed cough should be performed as needed, but at least every two to four hours when the presence of retained secretions is known. Universal precautions and infection control measures should always be considered as part of the treatment protocol.

Postural drainage therapy, percussion, and vibration

The relative merits of each type of physical therapy for airway clearance have been debated in the literature. Many individual, small, studies have not established whether the various modalities favorably impact clinical outcomes. A recent statement in *Chest* indicates that percussion and vibration are of no additional benefit to postural drainage.⁴ However, therapists sometimes find that these modalities help some of their patients, depending upon the individual patient's disease process, age, and other factors. So, what really works?

A meta-analysis by J. Thomas indicates that there were no differences between chest physical therapy modalities. These modalities include standard chest physical therapy (CPT),

which includes percussion and vibration; standard CPT with exercise; positive expiratory pressure therapy; FET; autogenic drainage; and the use of manual versus mechanical vibration/percussion. The study did establish, however, that standard CPT resulted in significantly more secretions expectorated than if no treatment were given at all.⁵

First and foremost, the need for postural drainage therapy and percussion/vibration should be assessed. Criteria for the need of such therapy include the assessment of excessive secretions, effective cough effort, pulmonary history, the character of breath sounds, chest x-ray, and oxygen saturation. These should be assessed together in order to make an informed decision regarding the type and combination of therapy indicated. Chest physical therapy includes the previously discussed directed cough effort and is an integral part of the procedure.

It is essential for the therapist to instruct the patient in effective cough technique. Postural drainage requires the effect of gravity by placing the targeted lung segment in position superior to the carina. Each position should be held for three to 15 minutes. Percussion may be applied to the chest wall by a cupped hand or mechanical device directly over the target segment. Vibration is performed by the application of fine tremorous action over the segment. The hands are placed in the direction of the ribs and the soft tissue. Pressure is applied during the expiratory maneuver. There is no conclusive evidence that any of these modalities are



more effective than the other when used in conjunction with postural drainage therapy.

Contraindications for the use of postural drainage therapy include head or neck injury, active bleeding, increased intracranial pressure (more than 20 torr), spinal injury, pulmonary edema, and hypertension. Vibration and percussion should not be administered to patients who have subcutaneous emphysema or spinal infusion/anesthesia, or those who have had recent thoracic surgery or injury.

The most common complication of postural drainage therapy is hypoxemia. Supplemental oxygen should be administered during treatment in those cases. Autogenic drainage may be instituted if this becomes a significant problem. Hypotension, increased intracranial pressure, pulmonary hemorrhage, arrhythmia, and pain are all complications that call for discontinuance of the procedure and consultation with the physician.

The patient's response to the treatment should be closely monitored. Certainly pain, discomfort, heart rate/rhythm, skin color, and oxygen saturation should be assessed before, during, and after treatment.

A positive outcome may be indicated by an increase in secretion production, improvement in breath sounds, increased oxygen saturation, improved chest x-ray, and the patient's own response to the treatment. The frequency of the treatment is best determined by the positive outcomes listed and a change in the overall status of the patient. Universal precautions and infection control

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guidelines should always apply during treatment.

It is essential for the therapist to continually reassess the modalities' effectiveness for each individual patient because some patients may respond positively while others may not.

Mucolytics and hydration

Each mucolytic drug available can be discussed in great detail. The primary purpose of these agents is to thin secretions and facilitate their removal from the airways. Mucus consists of a mixture of glycoproteins, proteoglycans, lipids, and deoxyribonucleic acid. The glycoproteins and proteoglycans are the substances that give mucus its viscosity. The most common forms of mucolytics are the use of cysteines and glycyl guaiacolate. Cysteines break the disulfide bonds that link glycoproteins. This decreases both the

viscosity and the elasticity of the secretions. Although the secretions may be thinner, the volume expectorated is not increased by the use of acetylcysteine.

Bromhexine (Ambroxol), used extensively in Europe and the United Kingdom, is known to reduce viscosity of secretions and aid in mucociliary clearance. Bromhexine acts by direct stimulation of the mucus-producing glands. Most of the studies done on the use of bromhexine are of a short treatment duration and therefore inconclusive. Dornase has had some success in decreasing viscosity of secretions. It is most effective when the secretions are purulent. Dornase is also thought to be helpful in antimicrobial therapy.³

An important factor to remember with any mucolytic is that they are known to cause

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Asthma Pharmacology

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past 25 years to treat asthma.² Demonstrating further benefits of this new class of drugs is a challenge respiratory therapists should embrace to improve the care of the asthmatic population. ♪

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Mechanical Ventilation

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Generally, the newer generation of ventilators do not deliver helium mixtures well because their internal gas-metering devices are not calibrated to such mixtures. Volume measurements (both inspiratory and expiratory) are usually subject to error. Therefore, it may be more reasonable to use pressure-limited, time-cycled modes of ventilation when using heliox. However, great care must be exercised when using mechanical ventilators to deliver low-density gases.

Airways Inflammation

Inflammation of the airways should be treated with steroids. As mentioned above, the therapist should closely monitor the interactions between steroids and other drugs being used. While there is a potential for re-

duced side effects with the use of topical steroids, no health care facility can avoid parenteral administration of steroids in status asthmaticus.

Finally, mucous plugging in the ventilated asthmatic needs to be treated. This is most easily done with hydration, both systemic and to the airways. As noted above, an 8 mm or larger endotracheal tube should be used whenever possible. Heated humidification of the ventilator circuit is extremely important. Therapeutic bronchoscopy may be indicated to treat segmental or lobar collapse. This is a treatment that is far from benign and should be done only by those who are familiar with both the technique and the risks associated with it.

Successful, safe ventilation of the patient suffering from status asthmaticus is challenging, but by no means impossible. ♪

Nicholas Widder is a lead therapist at the Carolinas Medical Center in Charlotte, NC. He received the AARC's Adult Acute Care Practitioner of the Year Award in 1997 and currently serves as the editor of the *Adult Acute Care Section Bulletin*.

Clearing Airways

(continued from page 71)

bronchospasm. A bronchodilator should always be given in conjunction with the administration of these agents. Guafenesin acts by irritating the stomach lining, resulting in stimulation of the vagus nerve. As the vagus nerve is stimulated, the bronchial glands begin to secrete fluid. This fluid will dilute the mucous blanket, thinning

out secretions and facilitating expectoration. Critics feel that guaifenesin is no more effective than water.

Increasing hydration is perhaps the best method to thin secretions and prevent mucous plugging. Unless contraindicated, a patient with thick, retained, or plug-type secretions would benefit from increasing water intake to 10 to 12 eight- to 10-ounce glasses per day. Coffee, tea, and cola with caffeine will promote water loss. Antihistamines, cough suppressants, and diuretics dry the body out and will make secretions more difficult to expectorate.

Increased water intake when using these substances is recommended. Alcohol should always be avoided, as this will enhance dehydration. Fruit juices and carbonated beverages will add a degree of hydration but cannot be expected to deliver the same effect as water. ♪

Janet C. Scialani is coordinator of the pulmonary rehabilitation program at Sarasota Memorial Hospital in Sarasota, FL. She currently serves on the board of directors of the American Lung Association of Gulfcoast Florida.

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Mailing December 13, 2001 Serial No.: Unassigned
Date: _____
File No.: 017534-000730 Attorney: JMH/jke
Applicant: Rodney A. Perkins
Title: METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME
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UTILITY PATENT APPLICATION TRANSMITTAL		Attorney Docket No. 017534-000730US	
		First Inventor	PERKINS, RODNEY A.
		Title	METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION
(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))		Express Mail Label No.	EL 387640039US
APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning design patent application contents.</i>		ADDRESS TO Assistant Commissioner for Patents Box Patent Application Washington, DC 20231	
<div>1. <input checked="" type="checkbox"/> Fee Transmittal Form (e.g., PTO/SB/17) <i>(Submit an original and a duplicate for fee processing)</i></div> <div>2. <input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.</div> <div>3. <input checked="" type="checkbox"/> Specification [Total Pages 17] <i>(preferred arrangement set forth below)</i><ul style="list-style-type: none">- Descriptive title of the Invention- Cross References to Related Applications- Statement Regarding Fed sponsored R & D- Reference to sequence listing, a table, or a computer program listing appendix- Background of the Invention- Brief Summary of the Invention- Brief Description of the Drawings (if filed)- Detailed Description- Claim(s)- Abstract of the Disclosure</div> <div>4. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets 16]</div> <div>5. Oath or Declaration [Total Pages 2]<div style="margin-left: 20px;"><div>a. <input type="checkbox"/> Newly executed (original or copy)</div><div>b. <input checked="" type="checkbox"/> Copy from a prior application (37 CFR 1.63 (d)) <i>(for a continuation/divisional with Box 18 completed)</i><div style="margin-left: 20px;">i. <input type="checkbox"/> DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).</div></div></div><div>6. <input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76</div></div>		<div>7. <input type="checkbox"/> CD-ROM or CD-R in duplicate, large table or Computer Program (<i>Appendix</i>)</div> <div>8. Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, all necessary)</i><div style="margin-left: 20px;"><div>a. <input type="checkbox"/> Computer Readable Form (CRF)</div><div>b. Specification Sequence Listing on:<div style="margin-left: 20px;">i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or</div>ii. <input type="checkbox"/> paper number of pages</div></div></div> <div>c. <input type="checkbox"/> Statements verifying identity of above copies</div>	
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Filing Date	December 13, 2001
First Named Inventor	PERKINS, RODNEY A.
Examiner Name	Unassigned
Group Art Unit	Unassigned
Attorney Docket No.	017534-000730US

TOTAL AMOUNT OF PAYMENT (\$) 370

METHOD OF PAYMENT		FEE CALCULATION (continued)																																																																																																																																																																															
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SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	James M. Heslin	Registration No. (Attorney/Agent)	29,541	Telephone	650-326-2400
Signature		Date	December 13, 2001		

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DECLARATION

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION** the specification of which X is attached hereto or was filed on as Application No. and was amended on (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56. I claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Country	Application No.	Date of Filing	Priority Claimed Under 35 USC 119

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date

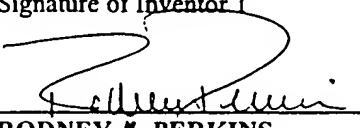
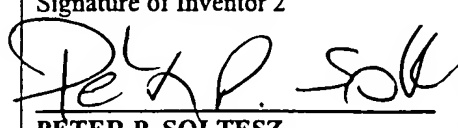
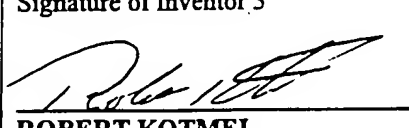
I claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Date of Filing	Status

Full Name of Inventor 1:	Last Name: PERKINS	First Name: RODNEY	Middle Name or Initial: A.
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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1 	Signature of Inventor 2 	Signature of Inventor 3 
RODNEY A. PERKINS	PETER P. SOLTESZ	ROBERT KOTMEL
Date ^{C.} 6/30/99	Date 07/01/99	Date 7/1/99

I hereby certify that this correspondence is being deposited with the United States Postal Service with "Express Mail Post Office to Address" service under 37 CFR 1.10 on this date of December 13, 2001, and is addressed to

PATENT
Attorney Docket No.: 017534-000730US

Assistant Commissioner for Patents
Washington, D.C. 20231

TOWNSEND and TOWNSEND and CREW LLP

By: 

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RODNEY A. PERKINS et al.

Application No.: Unassigned

Filed: Herewith

For: METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION

Examiner: Unassigned

Art Unit: Unassigned

PRELIMINARY REMARKS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-referenced application, please enter the following remarks.

REMARKS

This application is a continuation of application no. 09/606,320, filed on June 28, 2000, which was a continuation-in-part of application no. 09/347,032, filed on July 2, 1999. The text of the specification of the present application is identical to that of application no. 09/347,032, and it is respectfully submitted that all claims herein are fully supported by the July 2, 1999, filing.

Claims 1 and 2 herein have been copied from claims 9 and 10 of U.S. Patent No. 6,258,100, which issued on July 10, 2001, from an application filed on October 10, 2000, and which claimed to be a divisional of application no. 09/379,972, filed on August 24, 1999.

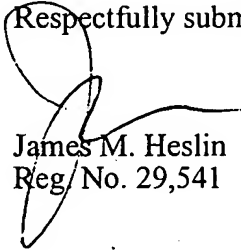
RODNEY A. PERKINS et al.
Application No.:
Page 2

PATENT

It is believed that all claims herein are entitled to an earlier priority date than that of the claims in the '100 patent.

If for any reason the Examiner believes that a telephone conference would in any way expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 650-326-2400.

Respectfully submitted,



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PA 3190039 v1

Application Data Sheet

Application Information

Application number::	Unassigned
Filing Date::	December 13, 2001
Application Type::	Regular
Subject Matter::	Utility
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Attorney Docket Number::	017534-000730US
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Total Drawing Sheets::	16
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Latin name::	
Variety denomination name::	
Petition included?::	No
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers One::	
Secrecy Order in Parent Appl.::	No

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Correspondence Information

Correspondence Customer Number:: 20350

Representative Information

Representative Customer Number:: 20350

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation of	09/606,320	06/28/00
	Continuation-in-part of	09/347,032	07/02/99

Foreign Priority Information

Country::	Application number::	Filing Date::
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PA 3190125 v1

PATENT APPLICATION

METHODS, SYSTEMS, AND KITS

FOR LUNG VOLUME REDUCTION

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METHODS, SYSTEMS, AND KITS FOR LUNG VOLUME REDUCTION

CROSS-REFERENCES TO RELATED APPLICATIONS

- 5 [01] This application is a continuation of application no. 09/606,320 (Attorney Docket No. : 17534-000710), filed on June 28, 2000, which was a continuation-in-part of application no. 09/347,032 (Attorney Docket No. 17534-000700), filed on July 2, 1999, now U.S. Patent No. 6,287,290, the full disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

- 10 [02] Field of the Invention. The present invention relates generally to medical methods, systems, and kits. More particularly, the present invention relates to methods and apparatus for effecting lung volume reduction by aspirating isolated segments of lung tissue.
- [03] Chronic obstructive pulmonary disease is a significant medical problem affecting 16 million people or about 6% of the U.S. population. Specific diseases in this group include chronic obstructive bronchitis, asthmatic (without bronchitis), and emphysema. While a number of therapeutic interventions are used and have been proposed, none are completely effective, and chronic obstructive pulmonary disease remains the fourth most common cause of death in the United States. Thus, improved and alternative treatments and therapies would be of significant benefit.
- 20 [04] Of particular interest to the present invention, lung function in patients suffering from chronic obstructive pulmonary disease can be improved by reducing the effective lung volume, typically by resecting diseased portions of the lung. Resection of diseased portions of the lungs both promotes expansion of the non-diseased regions of the lung and decreases the portion of inhaled air which goes into the lungs but is unable to transfer oxygen to the blood. Lung reduction is conventionally performed in open chest or thoroscopic procedures where the lung is resected, typically using stapling devices having integral cutting blades.
- 25 [05] While effective in many cases, conventional lung reduction surgery is significantly traumatic to the patient, even when thoroscopic procedures are employed.
- 30 Such procedures often result in the unintentional removal of healthy lung tissue, and frequently leave perforations or other discontinuities in the lung which result in air leakage

from the remaining lung. Even technically successful procedures can cause respiratory failure, pneumonia, death, and many older or compromised patients are not even candidates for these procedures. For these reasons, it would be desirable to provide improved methods, systems, and kits for performing lung volume reduction which overcome at least some of the shortcomings noted above.

[06] Description of the Background Art. WO 99/01076 describes devices and methods for reducing the size of lung tissue by applying heat energy to shrink collagen in the tissue. In one embodiment, air may be removed from a bleb in the lung to reduce its size. Air passages to the bleb may then be sealed, e.g., by heating, to fix the size of the bleb. WO 98/49191 describes a plug-like device for placement in a lung air passage to isolate a region of lung tissue, where air is not removed from the tissue prior to plugging. WO 98/48706 describes the use of surfactants in lung lavage for treating respiratory distress syndrome.

[07] Patents and applications relating to lung access, diagnosis, and treatment include U.S. Patent Nos. 5,752,921; 5,707,352; 5,682,880; 5,660,175; 5,653,231; 5,645,519; 5,642,730; 5,598,840; 5,499,625; 5,477,851; 5,361,753; 5,331,947; 5,309,903; 5,285,778; 5,146,916; 5,143,062; 5,056,529; 4,976,710; 4,955,375; 4,961,738; 4,958,932; 4,949,716; 4,896,941; 4,862,874; 4,850,371; 4,846,153; 4,819,664; 4,784,133; 4,742,819; 4,716,896; 4,567,882; 4,453,545; 4,468,216; 4,327,721; 4,327,720; 4,041,936; 3,913,568 3,866,599; 3,776,222; 3,677,262; 3,669,098; 3,498,286; 3,322,126; WO 95/33506, and WO 92/10971.

[08] Lung volume reduction surgery is described in many publications, including Becker et al. (1998) Am. J. Respir. Crit. Care Med. 157:1593-1599; Criner et al. (1998) Am. J. Respir. Crit. Care Med. 157:1578-1585; Kotloff et al. (1998) Chest 113:890-895; and Ojo et al. (1997) Chest 112:1494-1500.

[09] The use of mucolytic agents for clearing lung obstructions is described in Sclafani (1999) AARC Times, January, 69-97. Use of a balloon-cuffed bronchofiberscope to reinflate a lung segment suffering from refractory atelectasis is described in Harada et al. (1983) Chest 84:725-728.

BRIEF SUMMARY OF THE INVENTION

[10] The present invention provides improved methods, systems, and kits for performing lung volume reduction in patients suffering from chronic obstructive pulmonary disease or other conditions where isolation of a lung segment or reduction of lung volume is desired. The methods are minimally invasive with instruments being introduced through the mouth (endotracheally) and/or in some cases through the chest, (e.g., thoracoscopically), and

rely on isolating the target lung tissue segment from other regions of the lung. Isolation is usually achieved by introducing an isolation/access catheter endotracheally to the air passages of a lung. By positioning a distal end of an isolation/access catheter within an air passage which opens into a target lung tissue segment, the segment may be isolated by occluding the air passage, typically by inflating an occlusion balloon or other structure on the catheter within the air passage. The target lung tissue segment may then be collapsed by aspirating air (and any other gases or liquids that may have been introduced) from the segment, typically through a lumen in the isolation/access catheter. Optionally, the air passage may then be sealed, for example by deploying a plug within the air passage. Suitable plugs include swellable collagen matrices which hydrate and expand within the air passage so that they fully occlude the passage. Other sealing methods include the use of tissue adhesives, such as fibrin glues, cyanoacrylate, etc.; the use of occlusive balloons; the use of self-expanding meshes, coils, and other occlusive structures; the use of energy-induced tissue fusion, such as radiofrequency tissue closure; and the like.

[11] In a first particular aspect of the methods of the present invention, air flow through and from the target lung tissue segment will be enhanced prior to aspiration of the segment. It is an objective of the present invention to aspirate and reduce the volume of the lung tissue segment as completely as possible. In one instance, obstructions to gas flow within the target tissue segment are reduced prior to or during aspiration of the segment.

Mucus and other obstructions within the target lung tissue segment (which is diseased and frequently subject to blockages) will interfere with substantially complete aspiration of the segment unless removed, disrupted, or otherwise addressed. In a second instance, where a lack of lung surfactant is a cause of the impeded air flow, the present invention will provide for administering a suitable surfactant prior to or during aspiration of the target lung tissue segment.

[12] In a first specific instance, the present invention reduces gas flow obstructions by inflating the lung tissue segment to a pressure higher than normal respiratory inflation pressures. Optionally, portions or segments of the lung adjacent to the target lung segments may be partially deflated or under-ventilated at the same time that the target segment is being inflated at a higher than normal pressure. For example, airflow into adjacent lung segments can be partially blocked to lower pressure in those segments, causing those segments to partially collapse. In a specific instance, a balloon can be used to partially block the bronchus of the lung with the target lung tissue segment.

[13] Usually, the isolated lung tissue segment will be inflated to a pressure in the range from 60 cm H₂O to 200 cm H₂O, preferably in the range from 100 cm H₂O to 150 cm H₂O, usually during the administration of general anesthesia (positive pressure ventilation). If a local anesthesia is being used, the pressure will usually be in the range from 10 cm H₂O to 100 cm H₂O, preferably from 30 cm H₂O to 60 cm H₂O. The duration of such "over inflation" will typically be in the range from one second to 600 seconds, preferably being in the range from 5 seconds to 60 seconds. Such lung inflation may be repeated more than one time. For example, the lung inflation may be carried out by inflating the isolated lung tissue segment in a pulsatile fashion. Over inflation will usually be performed using the isolation/access catheter which was used to isolate the lung tissue segment. Optionally, it would be possible to inflate regions of the lung percutaneously using a needle introduced through the chest, typically under thoracoscopic observation.

[14] In a second specific instance, gas flow obstructions within the target lung tissue segment may be reduced by introducing an agent which clears the obstructions and/or dilates the air passages to permit gas flow around any blockages. Exemplary agents include mucolytic agents, bronchodilators, surfactants, desiccants, solvents, necrosing agents, absorbents, and the like. Such agents may be introduced through a catheter, typically through the isolation/access catheter which has been used to isolate the target lung tissue segment. Optionally, such agents may be heated, typically to a temperature in the range from 38°C to 90°C to enhance activity.

[15] In a third specific instance, gas flow obstructions are reduced by delivering mechanical energy to the lung segment, typically vibratory energy which will break down at least some of the obstructions. Typically, the vibratory energy will be ultrasonic energy, more typically being ultrasonic energy having a frequency in the range from 20 kHz to 20 MHz, usually from 20 kHz to 5 MHz. The mechanical energy will usually be delivered to the target lung tissue segment through a non-compressible fluid introduced to the segment, usually through the isolation/access catheter. It will be appreciated that air is a poor transmission and absorption material for ultrasonic and other vibratory energy. Thus, introducing a non-compressible fluid, such as saline, contrast medium, treatment solution (e.g., mucolytic solution, surfactant solution, etc.), or the like, will enhance transmission and absorption of the energy throughout the target lung tissue segment. The vibratory energy may then be applied either through a catheter which has been introduced endotracheally and then into the target lung tissue segment, or externally using a hand-held or other ultrasonic probe intended to deliver ultrasonic energy transcutaneously. Typically, the vibrational

treatment will last for time in the range from 5 seconds to 60 minutes, usually from 30 seconds to 30 minutes.

[16] In a second aspect of the methods of the present invention, collapse of the target isolated lung tissue segment is enhanced by applying external pressure to the isolated segment. The external pressure will usually be applied through the chest, e.g., thoracoscopically. Most simply, a needle can be introduced to a pleural space over the lung, typically intracostally (between adjacent ribs). The pleural space can then be insufflated, e.g., carbon dioxide or other gas inflation medium introduced to the pleural space, in order to increase pressure on the lung and enhance collapse of the target segment. Simultaneously, the target segment will be aspirated so that the combined lowering of the internal pressure and raising of the external pressure work to substantially completely collapse the segment. Alternatively, the external pressure may be applied by inflating a balloon in the pleural space over the target lung tissue segment. Still further optionally, the external pressure may be applied by a probe which is engaged and pushed against at least a portion of the external surface of the lung overlying the target segment. Optionally, a thoracoscopically or other percutaneously placed needle could be used to puncture and aspirate a portion of the lung, typically in conjunction with a catheter-based aspiration as described elsewhere herein. For example, portions of the lung which could not be collapsed using an internal catheter could be targeted with an external needle by thoracoscopic visualization. Any puncture holes left in the lung could then be sealed with a suitable adhesive, such as a fibrin glue.

[17] In a third aspect of the present invention, methods for reducing lung volume by isolating the lung tissue segment and aspirating the isolated segment are combined with diagnostic methods which permit, for example, determination of whether the segment which has been accessed and isolated is in fact diseased and should be collapsed. The diagnostic methods and steps may take a wide variety of forms. For example, the isolation/access catheter or other endotracheally introduced catheter may be used to measure air flow to and from the lung tissue segment to determine whether the air flow capabilities of that segment are impaired. Alternatively or additionally, the isolation/access catheter may be used to measure carbon dioxide concentrations within the target lung tissue segment. Other parameters which may be measured include forced expiratory volume, pressure, pressure/volume P/V curves, segment compliance curves, work of breathing data, perfusion scans, bronchograms, or the like.

[18] In a still further aspect of the methods of the present invention, a target lung tissue segment is isolated and aspirated, where the segment is collapsed to a volume which is

no greater than 40% of its inflated size prior to aspiration, usually being no greater than 30%, and preferably being no greater than 20%. The inflated size is its maximum size at normal spontaneous respiratory pressures, assumed to be 40 cm H₂O for patients undergoing positive pressure ventilation, the spontaneous respiratory pressure is assumed to be 90 cm H₂O. The change in volume may be determined by conventional techniques, such as thoracoscopy (X-ray), CT scans, MRI, ultrasound imaging, bronchograms, and the like.

[19] Such efficient collapsing of the target lung tissue segment may be achieved in any of the ways discussed above. Additionally, it may be achieved by inducing absorption atelectasis prior to aspiration. Most simply, absorption atelectasis can be induced by insufflating the isolated lung tissue segment with high oxygen concentrations prior to aspiration. The oxygen concentrations in the insufflation gas should be at least 50% by volume, preferably 75% by volume, and more preferably being substantially pure oxygen.

[20] The present invention further provides systems for performing intraluminal lung volume reduction procedures according to the methods of the present invention. The systems comprise at least an isolation or access catheter having a proximal end, a distal end, an occlusion element near the distal end, and at least one lumen therethrough. The isolation/access catheters are used for establishing access and isolation of a target lung tissue segment, typically by endotracheal introduction into the air passages of the lung. In a first system according to the present invention, the isolation/access catheter is combined with a sealing catheter which carries a closure element. A sealing catheter is adapted to be introduced through the lumen of the isolation/access catheter, and the closure element is adapted to be deployed from the isolation/access catheter within an air passage leading to the target tissue segment. The closure element typically comprises a swellable plug, such as a partially hydrated collagen plug. Deployment within the air passage thus permits the plug to swell in situ and completely block the air passage leading into the target tissue segment so that, once the segment is collapsed, air will not enter to reinflate the segment. Surprisingly, it has been found that such occlusion will substantially inhibit reinflation of the lung, and that there is little significant collateral air flow into the collapsed region.

[21] In a second aspect, the systems of the present invention will combine the isolation/access catheter with a reagent capable of either clearing, dilating, or widening the air passages in order to facilitate substantially complete aspiration of the target tissue segments. Exemplary reagents have been set forth above.

[22] In a third aspect, the systems of the present invention will combine the isolation/access catheter with probes intended for percutaneous introduction to apply external

pressure over the lung. The probes may be in the form of a needle, a balloon, or a simple engagement element intended for pressing inwardly against the lung.

[23] The present invention still further comprises kits which include at least an isolation/access catheter as described above. The kits will further comprise instructions for use according to any of the methods set forth above. For example, the instructions for use may set forth that the isolated lung tissue segment is to be over inflated in order to reduce blockages therein. Alternatively, the instructions for use may set forth that certain agents (as described above) are to be introduced to the segment in order to breakdown obstructive materials prior to aspiration. Still further, the kit instructions may set forth that the lung is to be externally collapsed by applying pressure or other external force to a target tissue segment prior to or simultaneous with aspiration of that segment. Still further, the instructions may set forth that the volume of the target lung tissue segment is to be reduced by at least the percentages set forth above. In all cases, the kits will usually further comprise packaging, such as a pouch, tray, tube, box, or the like for holding the kit components together with the instructions for use. The instructions for use may be printed on a separate sheet (commonly referred to as a package insert) and/or may be printed on the packaging itself. Usually, the kit components which will be introduced to the patient will be sterilized and packaged in a sterile manner within the kit.

BRIEF DESCRIPTION OF THE DRAWINGS

[24] Fig. 1 is a perspective illustration of an isolation/access catheter useful in the methods, systems, and kits of the present invention.

[25] Fig. 2 is a cross-sectional view taken along line 2 to a Fig. 1.

[26] Figs. 3A-3F illustrate alternative cross-sectional views of the isolation/access catheter of Fig. 1.

[27] Figs. 4A-4C illustrate use of the isolation/access catheter of Fig. 1 for isolating and collapsing a target lung tissue segment according to the methods of the present invention.

[28] Fig. 4D illustrates one protocol for over inflating a target lung tissue segment prior to aspiration according to the present invention.

[29] Fig. 5 illustrates an optional aspect of the present invention where an insufflation gas is introduced to aid in the collapse of the target segment from the pleural space.

[30] Fig. 6 illustrates an alternative optional aspect of the present invention where an inflatable balloon is used to externally collapse a portion of a target lung tissue segment.

[31] Figs. 7A-7D illustrate alternative balloon designs for use in external collapse of the target lung tissue segment.

5 [32] Fig. 8 illustrates yet another alternative optional aspect of the methods of the present invention where a probe is used to engage and collapse a portion of a target lung tissue segment.

[33] Figs. 9A-9C illustrate alternative probe designs.

[34] Figs. 10A-10C illustrate a sealing catheter carrying a swellable closure
10 element which may be used in the methods, systems, and kits of the present invention.

[35] Fig. 11 illustrates use of the sealing catheter of Figs. 10A-10C for selectively occluding an air passage leading to a target lung tissue segment according to the methods of the present invention.

[36] Figs. 12A-12C illustrate a steerable imaging guidewire which may be used to
15 facilitate positioning of the isolation/access catheter used in the methods of the present invention.

[37] Fig. 13 illustrates a kit constructed in accordance with the principles of the present invention.

20 DETAILED DESCRIPTION OF THE INVENTION

[38] Lung volume reduction is performed by collapsing a target lung tissue segment, usually within sub-lobular regions of the lung which receive air through a single air passage, i.e., segment of the branching bronchus which deliver to and receive air from the alveolar regions of the lung. Such isolated lung tissue segments are first isolated and then
25 collapsed by aspiration of the air (or other gases or liquids which may have been introduced, as discussed below) from the target lung tissue segment. Lung tissue has a very high percentage of void volume, so removal of internal gases can reduce the lung tissue to a small percentage of the volume which it has when fully inflated, i.e. inflated at normal inspiratory pressures. The exemplary and preferred percentages for the volume reduction are set forth
30 above.

[39] In particular, the present invention provides methods and apparatus for enhancing the aspiration and collapse of the target lung tissue segment. Such methods and apparatus may involve one or more of the following improvements. First, various approaches may be taken to remove or lessen obstructions to gas flow within the target tissue region.

Second, methods and apparatus may be employed to apply external pressure over the lung to enhance the collapse achieved by internal aspiration. Third, aspiration of the gases within the target tissue segment may be enhanced by inducing absorption atelectasis prior to aspiration.

Absorption atelectasis may be induced, for example, by introducing an oxygen-rich gas to the lung tissue segment, usually at least 50% oxygen by weight, more usually at least 75% oxygen by weight, and preferably substantially pure oxygen. Absorption atelectasis is a phenomena which occurs when an enriched oxygen mixture is inspired. The high oxygen concentration causes an increase in the partial oxygen pressure which in turn causes the rate of oxygen transfer into the capillary blood within the alveolar regions to increase greatly.

The increased oxygen flux may increase so much that the net flow of gas into the blood exceeds the inspired flow of gas, causing the lung unit to become progressively smaller.

Fourth, the access methods and apparatus may be used for performing in situ diagnosis, usually as part of the collapse procedure. Any one of a number of lung performance characteristics may be measured, typically by sampling using the isolation/access catheter.

[40] The methods of the present invention will generally rely on accessing the target lung tissue segment using an isolation/access catheter adapted to be introduced endotracheally into the bronchus of the lung. An exemplary isolation/access catheter 10 is illustrated in Figs. 1 and 2 and comprises a catheter body 12 having a distal end 14, a proximal end 16, an inflatable occlusion balloon 18 near its distal end, and at least one lumen therethrough. Usually, the catheter will have at least two lumens, and catheter 10 includes both a central lumen 20 and an annular lumen 22 defined by inner body member 24 and outer body member 26 which is coaxially disposed about the inner body member. The annular lumen 22 opens to port 30 on a proximal hub 32 and provides for inflation of balloon 18. The central lumen 20 opens to port 36 on hub 32 and provides for multiple functions, including optional introduction over a guidewire, aspiration, introduction of secondary catheters, such as sealing catheters described below, and the like.

[41] The dimensions and materials of isolation/access catheter 10 are selected to permit endotracheal introduction and intraluminal advancement through the lung bronchus, optionally over a guidewire and/or through a primary tracheal tube structure (as illustrated in Fig. 4B below). Suitable materials include low and high density polyethylenes, polyamides, nylons, PTFE, PEEK, and the like, particularly for the inner tubular member 24. The outer member, including the occlusion balloon, can be made from elastomeric materials, such as polyurethane, low density polyethylene, polyvinylchloride, silicone rubber, latex, and the like. Optionally, portions of the outer tubular member 26 proximal to the inflatable balloon

can be made thicker and/or reinforced so that they do not dilate upon pressurization of the balloon. Exemplary dimensions for the isolation/access catheter 10 are set forth in the table below.

ISOLATION/ACCESS CATHETER DIMENSIONS				
	<u>Exemplary</u>		<u>Preferred</u>	
	Inner Tubular Member	Outer Tubular Member	Inner Tubular Member	Outer Tubular Member
Outer Diameter (mm)	0.4-4	0.6-4.5	1-1.5	2-4
Wall Thickness (mm)	0.05-0.25	0.5-0.25	0.1-0.2	0.15-0.25
Length (cm)	50-150	same	50-80	same
Balloon Length (mm)	5-50		10-20	
Balloon Diameter (mm) (inflated)	2-15		6-12	

5 [42] The isolation/access catheter 10 may be modified in a number of ways, some of which are illustrated in Figs. 3A-3F. For example, instead of a inner and outer coaxial tube construction, the catheter can be a single extrusion having a catheter body 30 with a circular main lumen 32 and a crescent-shaped inflation lumen 34, as illustrated in Fig. 3A. Alternatively, catheter body 40 may be formed as a single extrusion having three lumens, i.e.,

10 a primary lumen 42 for receiving a guidewire, applying aspiration, and/or delivering secondary catheters. A second lumen 44 can be provided for inflating the occlusion balloon, and a third lumen 46 can be provided as an alternative guidewire or aspiration lumen. Catheter body 50 comprising a main tubular body 52 having an outer layer 54 fused thereover to define a lumen 56 suitable for balloon inflation as shown in Fig. 3C. A primary lumen 58

15 is formed within the main tubular member 52. As a slight alternative, catheter body 60 can be formed from a primary tubular member 62, and a secondary tubular member 64, where the tubular members are held together by an outer member 66, such as a layer which is applied by heat shrinking. The primary tubular member 62 provides the main lumen 68 while secondary tube 64 provides a secondary lumen 70. The secondary lumen 70 will typically be

20 used for balloon inflation, while the primary lumen 68 can be used for all other functions of the isolation/access catheter.

[43] Optionally, the isolation/access catheter in the present invention can be provided with optical imaging capability. As shown in Fig. 3E, catheter body 80 can be

formed to include four lumens, typically by conventional extrusion processes. Lumen 82 is suitable for passage over a guidewire. Lumens 84 and 86 both contain light fibers 88 for illumination. Lumen 90 carries an optical wave guide or image fiber 92. Lumen 82 can be used for irrigation and aspiration, typically after the guidewire is withdrawn. Balloon inflation can be effected through the space remaining and lumens 84 and 86 surrounding the light fibers 88. A second catheter body 100 is formed as a coaxial arrangement of a number of separate tubes. Outer tube 102 contains a separate guidewire tube 104 defining lumen 106 which permits introduction over a guidewire as well as perfusion and aspiration after the guidewire is removed. Second inner tubular member 110 will carry an optical image fiber 112 and a plurality of light fibers 112 are passed within the remaining space 114 within the outer tubular member. In both catheter constructions 80 and 100, forward imaging can be effected by illuminating through the light fibers and detecting an image through a lens at the distal end of the catheter. The image can be displayed on conventional cathode-ray or other types of imaging screens. In particular, as described below, forward imaging permits a user to selectively place the guidewire for advancing the catheters through a desired route through the branching bronchus.

[44] Referring now to Fig. 4A, a catheter 10 can be advanced to a diseased region DR within a lung L through a patient's trachea T. Advancement through the trachea T is relatively simple and will optionally employ a guidewire to select the advancement route through the branching bronchus. As described above, steering can be effected under real time imaging using the imaging isolation/access catheters illustrated in Figs. 3E and 3F.

Optionally, the isolation/access catheter 10 may be introduced through a visualizing tracheal tube, such as that described in U.S. Patent No. 5,285,778, licensed to the assignee of the present application. The visualizing endotracheal tube 120 includes an occlusion cuff 122 which may be inflated within the trachea just above the branch of the left bronchus and right bronchus LB and RB, respectively. The visualizing endotracheal tube 120 includes a forward-viewing optical system, typically including both illumination fibers and an image fiber to permit direct viewing of the main branch between the left bronchus LB and right bronchus RB. Thus, initial placement of isolation/access catheter can be made under visualization of the visualizing endotracheal tube 120 and optionally the isolation/access catheter 10 itself. Referring again in particular to Fig. 4A, the isolation/access catheter 10 is advanced until its distal end 14 reaches a region in the bronchus which leads directly into the diseased region DR. Once in place, the balloon 18 can be inflated and the lung tissue segment which includes the diseased region isolated from the remainder of the lung. By

isolated, it is meant that air or other gases will not pass between the isolated region and the remaining portions of the lung to any significant extent.

[45] As shown in Fig. 4C, it is the object of the present invention to apply a vacuum to a lumen within the isolation/access catheter 10 to aspirate the internal regions within the isolated lung tissue segment in order to collapse the tissue. This results in a collapsed lung tissue region CLT, as shown as a shaded region in Fig. 4C.

[46] According to the present invention, a variety of steps and protocols may be performed prior to aspirating the isolated lung tissue region in order to enhance gas removal from the region. The region may be over inflated, subjected to vibrations, subjected to a dilating or mucolytic agent, or otherwise treated in order to remove gas flow obstructions within the region. Each of these methods has been well described above and will generally rely on performance of at least one aspect of the procedure using a lumen of the isolation/access catheter 10. For example, over inflation can be effected simply by introducing an inflation gas through the isolation/access catheter to a desired pressure.

Pressure may be measured using a transducer at the distal tip of the catheter 10, but will usually be measured statically at a location proximal of the catheter. Alternatively or additionally, an oxygen-rich gas can be introduced through the isolation/access catheter in order to induce absorption atelectasis. For vibratory stimulation incompressible fluid may be introduced through the isolation/access catheter. Stimulation may be imparted using an external probe and/or a vibratory catheter which is introduced through an access lumen of the isolation/access catheter.

[47] As shown in Fig. 4D, in some instances it will be desirable to reduce or selectively control the inflation of the lung tissue adjacent to the target lung tissue segment in order to enhance aspiration of the target segment. For example, an entire one-half lung can be selectively controlled by an isolation or shunting catheter having a balloon 132 near its distal end. The balloon is inflated to occlude a portion of the selected bronchus, typically about 60% of the area. Thus, pressure within the lung can be reduced and the lung partly collapsed other than in the isolated region. In this way, inflation of the target lung tissue segment can be enhanced which can assist in breaking up occlusions within the lung which would otherwise interfere with subsequent aspiration of the segment.

[48] In addition to such in situ techniques for enhancing lung aspiration and collapse, the present invention can rely on application of an external force to assist in collapse. As illustrated in Fig. 5, a needle or other cannula 200 can be percutaneously introduced into a peritoneal space PS between the parietal pleural PP and visceral pleural VP.

Insufflation gas, such as carbon dioxide, can be introduced through the needle 200, either using a syringe or other pressure source. The gas will typically be introduced to a pressure in the range from 30 cm H₂O to 200 cm H₂O in spontaneously breathing patients and 70 cm H₂O to 250 cm H₂O in positive pressure ventilated patients.

5 [49] Use of an unconstrained insufflation gas, however, is disadvantageous since it is not directed at a particular target location. In order to more specifically direct an external pressure against the lung, a balloon 210 can be introduced to the pleural space, typically through a thoracic trocar 212. The balloon can be placed based on fluoroscopic observation. Depending on the particular area which is to be collapsed, a variety of specific balloon
10 configurations can be employed, as illustrated in Figs. 7A-7D. A generally spherical balloon 220 is shown attached to shaft 220 in Fig. 7A. Other configurations include a winged profile (Fig. 7B), a cylindrical or spatula profile (Fig. 7C), and a convex profile (Fig. 7D). Each of these will be attached to a shaft which permits inflation after introduction into the pleural space.

15 [50] As a further alternative to needle insufflation and balloon expansion, a target lung tissue segment can be externally collapsed using a simple probe 250, usually introduced through a thoracic trocar 252, as shown in Fig. 8. A variety of probes for mechanically engaging and compressing the outer lung surface are illustrated in Figs. 9A-9C. Optionally, a needle can be used to puncture at a desired point in the target tissue lung segment in order to
20 release and/or aspirate air, usually as a supplement to a primary catheter-based aspiration. The puncture can then be sealed with fibrin glue or other suitable sealant.

[51] The methods of the present invention will optionally comprise sealing or occluding the air passage leading to the collapsed tissue region CLT. Such sealing can be performed in a variety of ways, including suturing, gluing, energy-mediated tissue adhesion,
25 and the like. In a preferred aspect of the present invention, a sealing catheter 280 can be used to deliver a plug 282, typically at partially hydrated collagen hydrogel, as illustrated in Figs. 10A-10C. Usually, the catheter will have dimensions which permit it to be introduced through the main access lumen of isolation/access catheter 10. The plug 282 will be contained in the distal tip of a lumen in the catheter, and a push rod 284 extends the length of
30 the catheter to permit the treating physician to deploy the plug 282 after the tip of the catheter is properly located, as illustrated in Fig. 11, usually while the balloon on the isolation/access catheter remains inflated and the target lung tissue remains sealed and in an aspirated, collapsed configuration. Once deployed within the moist environment of the lung bronchus,

the plug 282 will absorb water and will swell substantially, typically from 100% to 1000% in order to fully occupy and plug the air passage into the collapsed lung tissue region CLT.

[52] Positioning of the isolation/access catheter 10 within the lung can be performed using on-board optical imaging capability, as discussed above. Usually, positioning of a guidewire through the branching bronchus will be manipulated while viewing through the imaging components of the isolation/access catheter. In this way, the isolation/access catheter can be "inched" along by alternately advancing the guidewire and the isolation/access catheter. As an alternative to providing the isolation/access catheter with imaging, positioning could be done solely by fluoroscopy. As a further alternative, a steerable, imaging guidewire 300 (Figs. 12A-12C) could be used. The guidewire 300 includes a deflectable tip 302 which can be deflected in a single plane using push/pull ribbon 304. Usually, the tip will comprise a spring 306 to facilitate deflection. In addition to steerability, the guidewire 300 will include an optical imaging wave guide 310 and illuminating optical fibers 312, as best seen in cross-sectional view of Fig. 12C. Thus, the guidewire 300 can be steered through the branching bronchus to reach the target tissue segment using its own in situ imaging capability. Once the guidewire 300 is in place, an isolation/access catheter can be introduced to the target lung tissue segment as well. Since the guidewire has imaging capability, the isolation/access catheter need not incorporate such imaging. This can be an advantage since it permits the access lumen to be made larger since the catheter need not carry any optical wave guides.

[53] Referring now to Fig. 13, kits 400 according to the present invention comprise at least an isolation/access catheter 10 and instructions for use IFU. Optionally, the kits may further include any of the other system components described above, such as a balloon probe 210, a sealing catheter 280, a reagent container 420 (optionally including any of the dilating or mucolytic agents described above), or other components. The instructions for use IFU will set forth any of the methods as described above, and all kit components will usually be packaged together in a pouch 450 or other conventional medical device packaging. Usually, those kit components, such as isolation/access catheter 10, which will be used in performing the procedure on the patient will be sterilized and maintained sterilely within the kit.

Optionally, separate pouches, bags, trays, or other packaging may be provided within a larger package, where the smaller packs may be opened separately and separately maintain the components in a sterile fashion.

[54] While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Therefore, the

above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

WHAT IS CLAIMED IS:

- 1 1. A method of reducing lung size of a lung, the method including the
2 steps of:
3 inserting a conduit down a trachea, into a mainstem bronchus, into a bronchial
4 branch, and into a bronchial sub-branch communicating with a lung portion of the lung to be
5 reduced in size;
6 pulling a vacuum in the lung portion through the conduit to collapse the lung
7 portion; and
8 deploying an obstructing member in the bronchial sub-branch to preclude air
9 from being inhaled into the lung portion through the bronchial sub-branch.
- 1 2. The method of claim 1, wherein the deploying step includes feeding
2 the obstructing member down the conduit and into the bronchial sub-branch.
- 1 3. A method for lung volume reduction, said method comprising:
2 isolating a lung tissue segment;
3 aspirating the isolated segment to cause the segment to collapse; and
4 sealing an air passage which opens to the lung segment to inhibit reinflation of
5 the segment.
- 1 4. The method of claim 3, wherein sealing comprises deploying a plug in
2 the air passage.
- 1 5. The method of claim 4, wherein deploying comprises advancing the
2 plug through a catheter to the air passage.

**METHODS, SYSTEMS, AND KITS
FOR LUNG VOLUME REDUCTION**

ABSTRACT OF THE DISCLOSURE

Lung volume reduction is performed in a minimally invasive manner by isolating a lung tissue segment, optionally reducing gas flow obstructions within the segment, and aspirating the segment to cause the segment to at least partially collapse. Further optionally, external pressure may be applied on the segment to assist in complete collapse. Reduction of gas flow obstructions may be achieved in a variety of ways, including over inflation of the lung, introduction of mucolytic or dilation agents, application of vibrational energy, induction of absorption atelectasis, or the like. Optionally, diagnostic procedures on the isolated lung segment may be performed, typically using the same isolation/access catheter.

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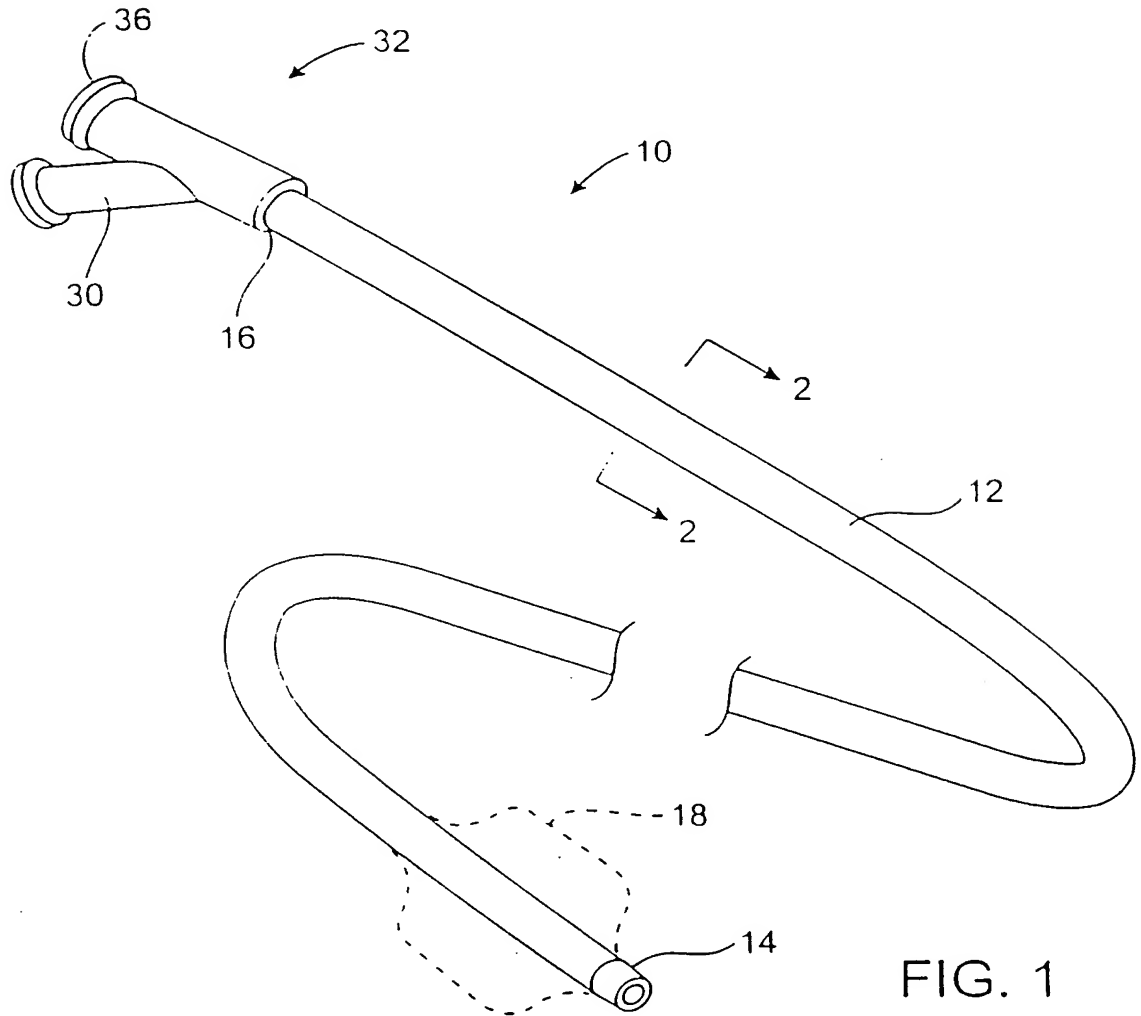


FIG. 1

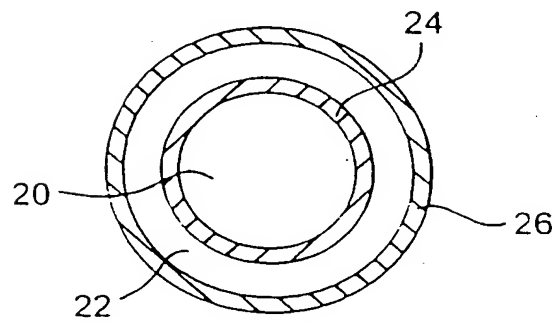


FIG. 2

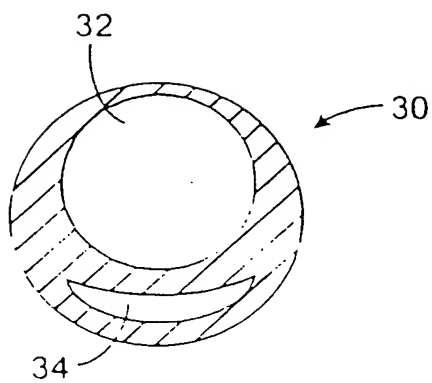


FIG. 3A

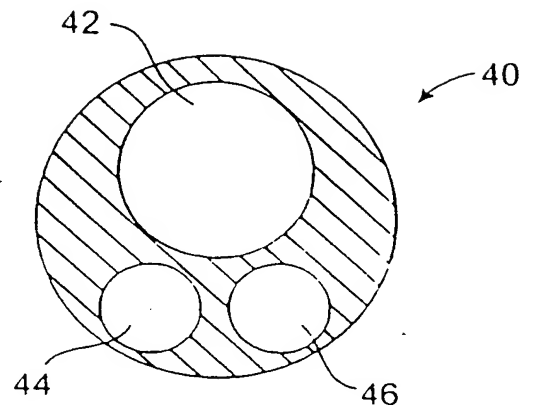


FIG. 3B

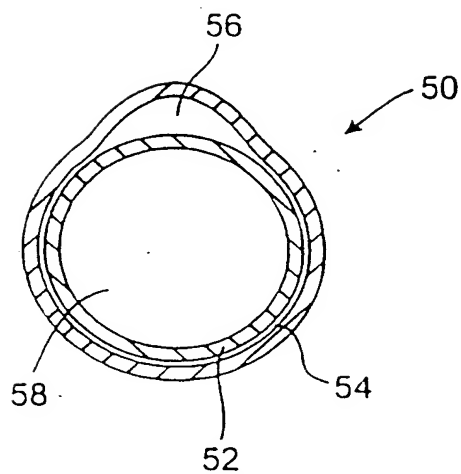


FIG. 3C

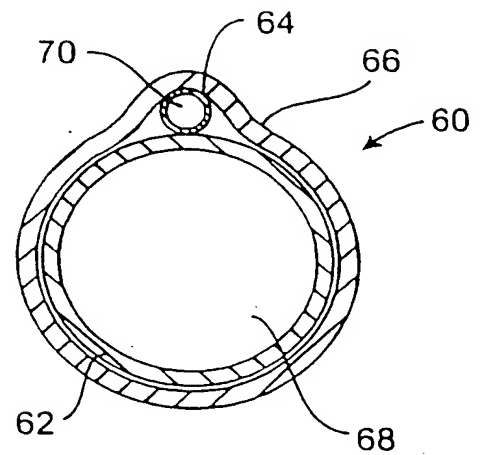


FIG. 3D

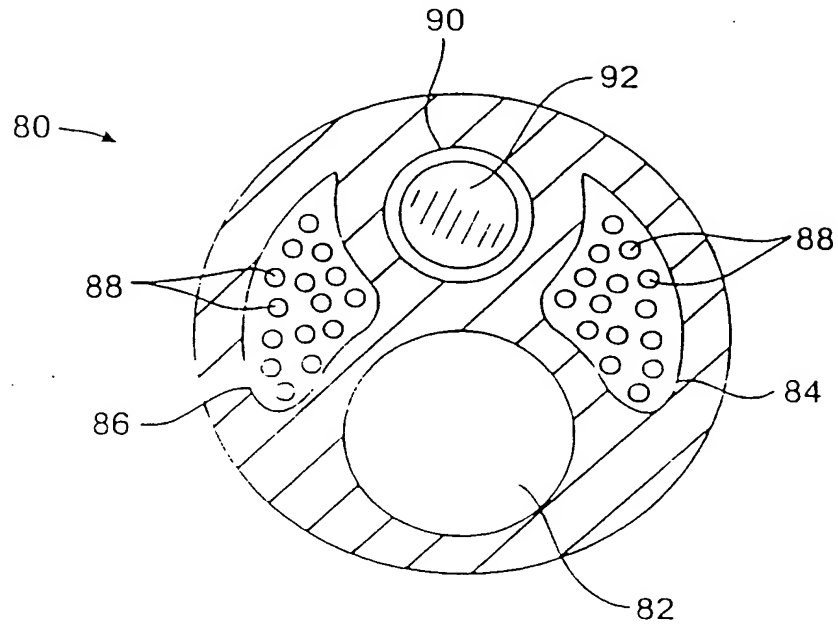


FIG. 3E

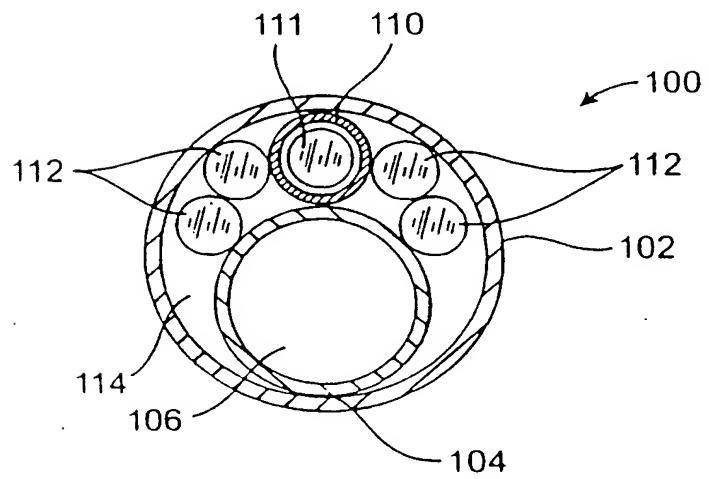


FIG. 3F

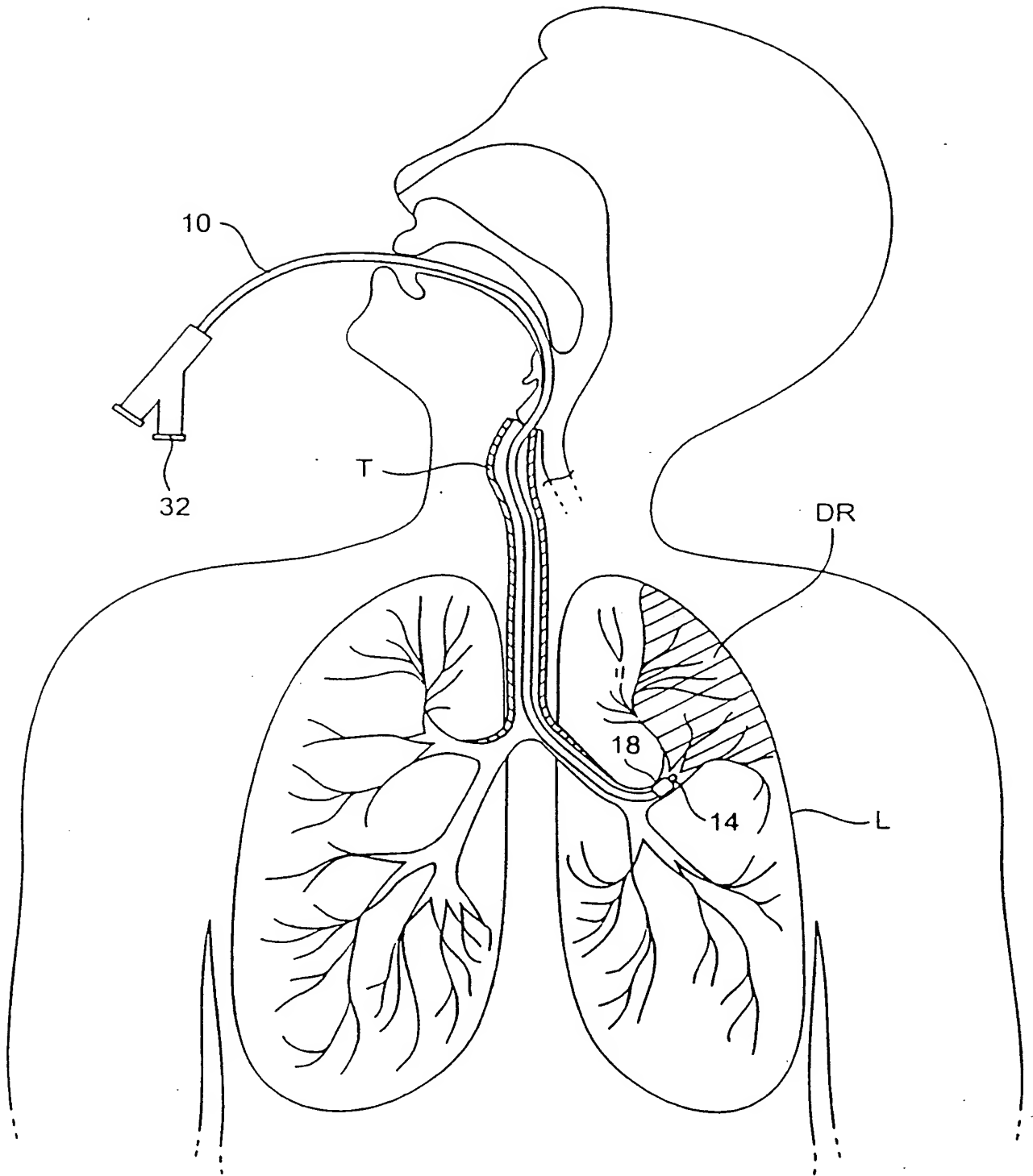


FIG. 4A

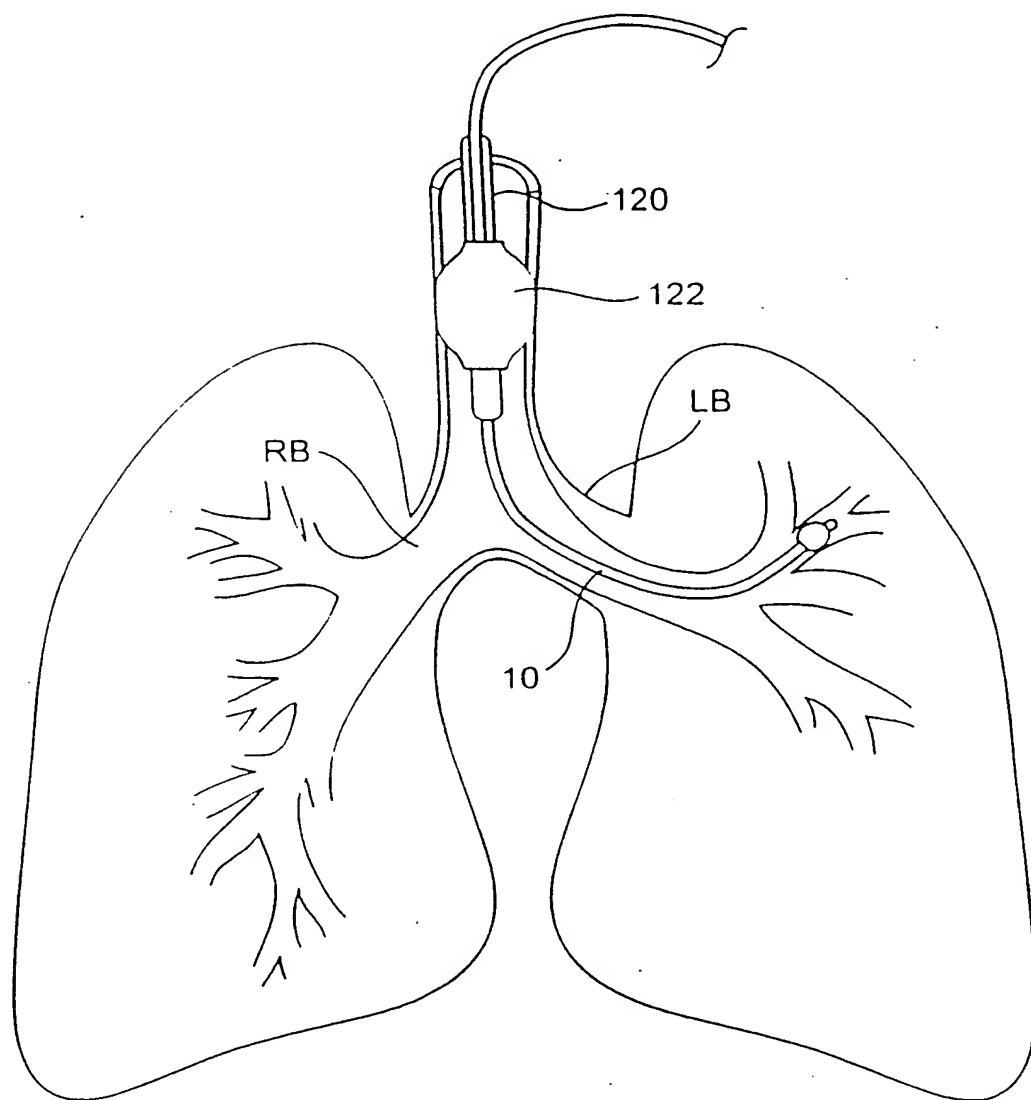


FIG. 4B

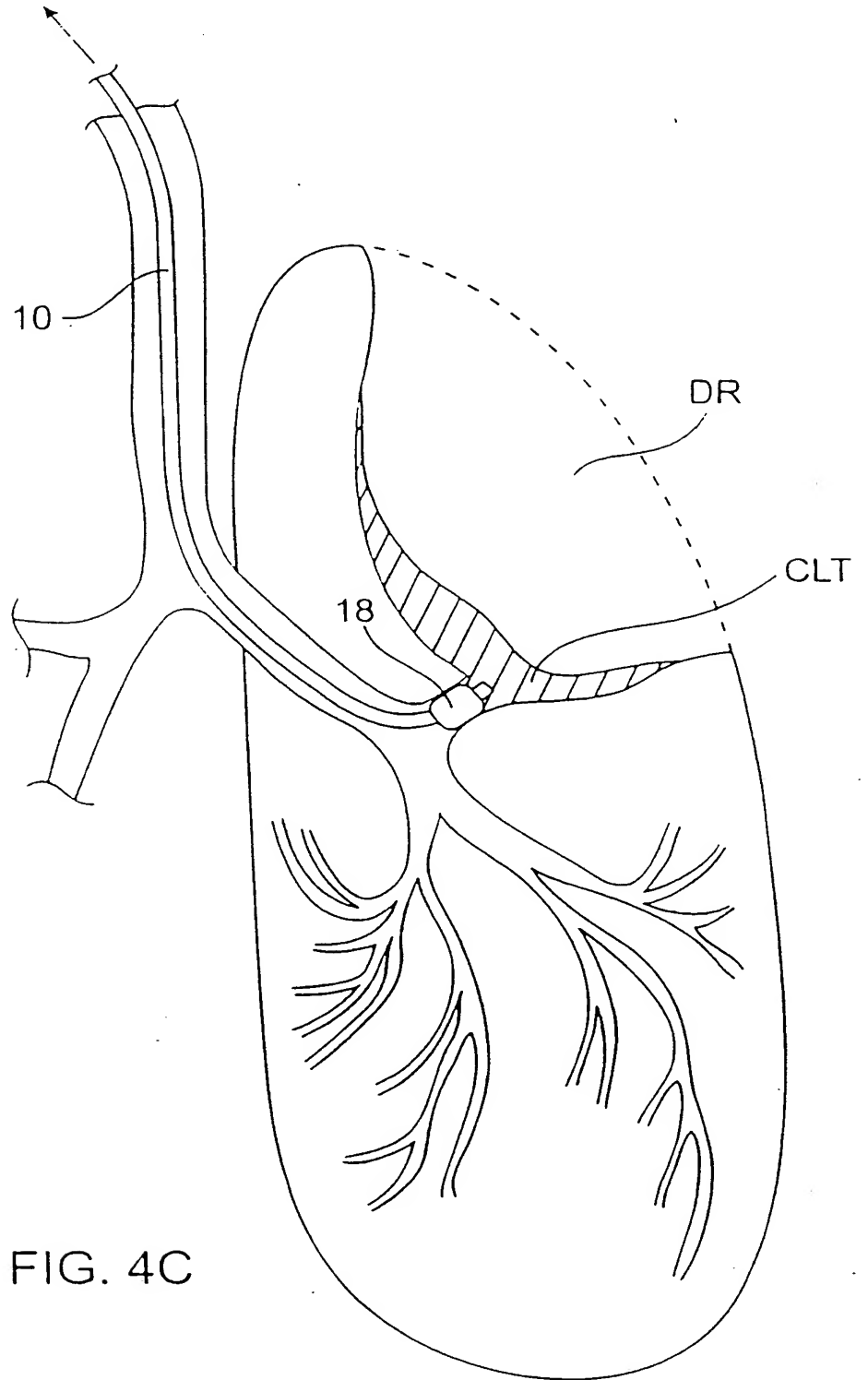


FIG. 4C

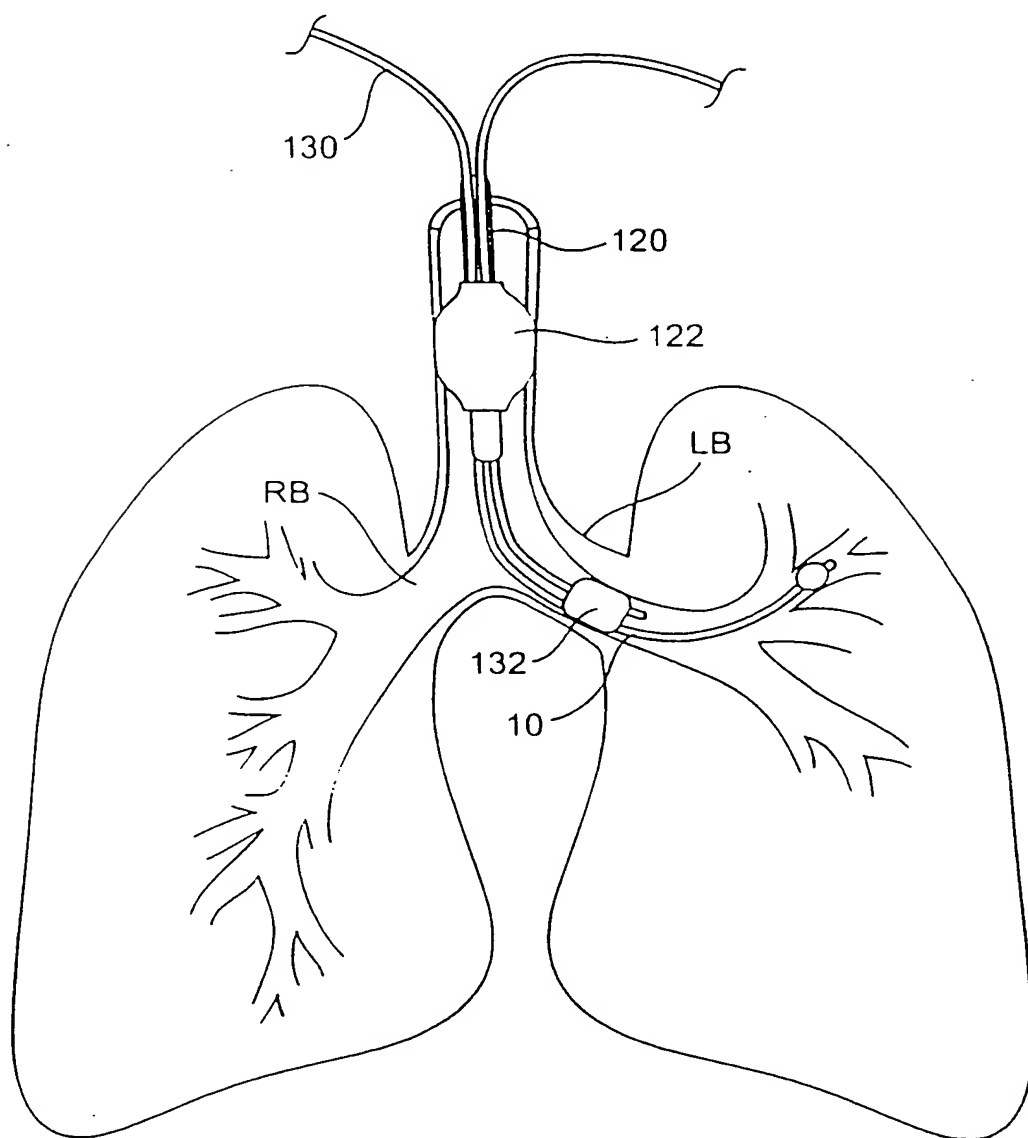


FIG. 4D

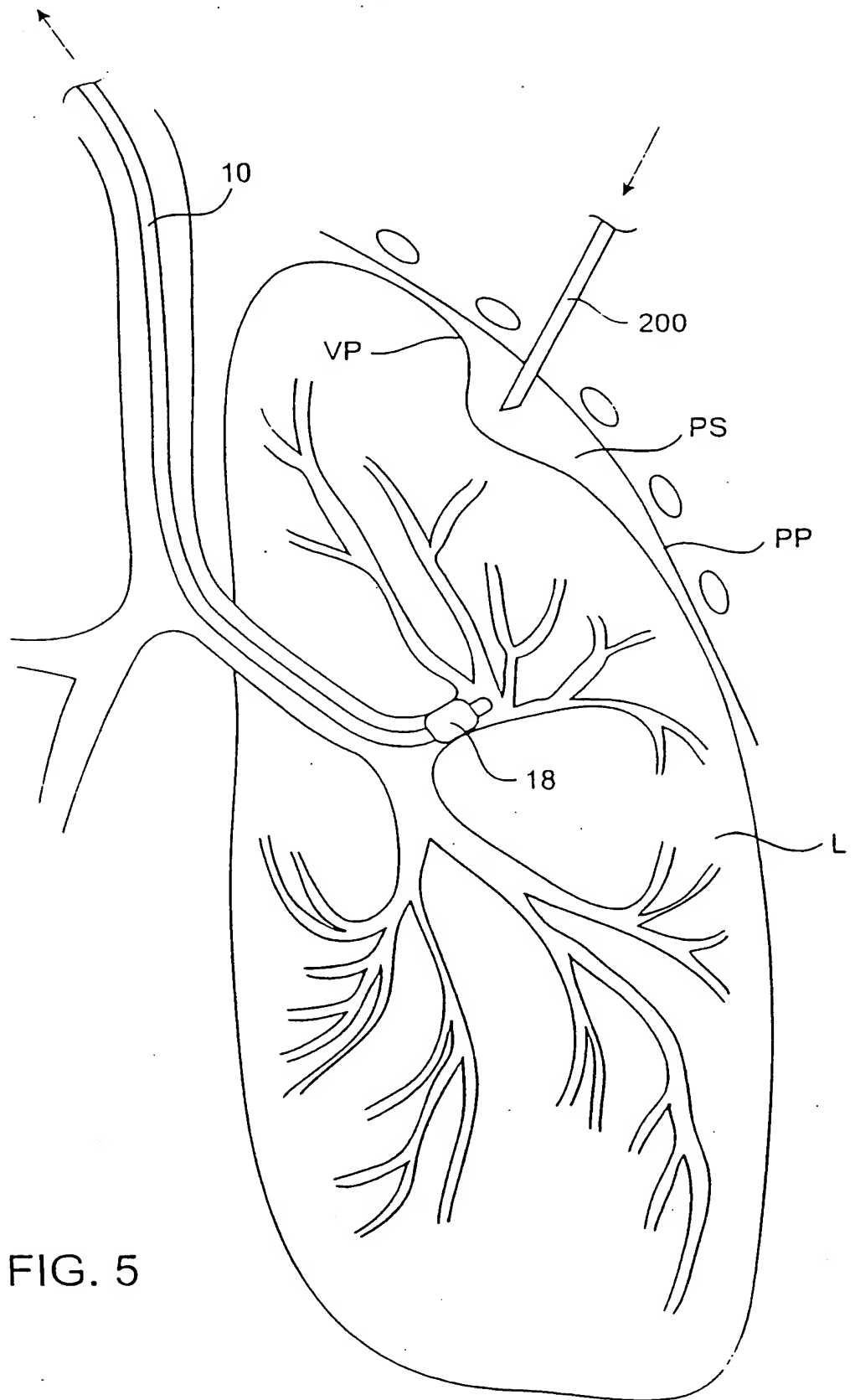


FIG. 5

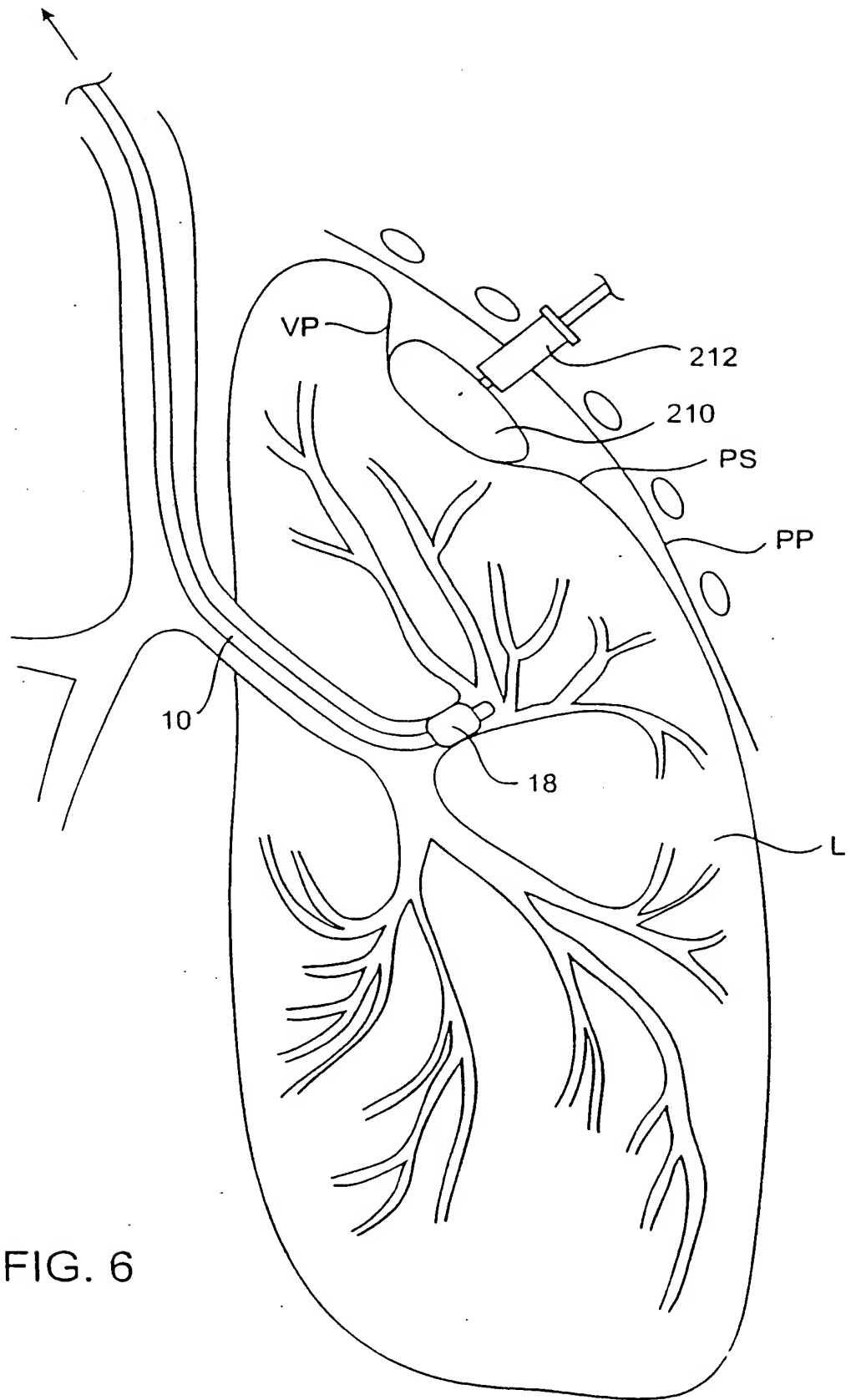


FIG. 6

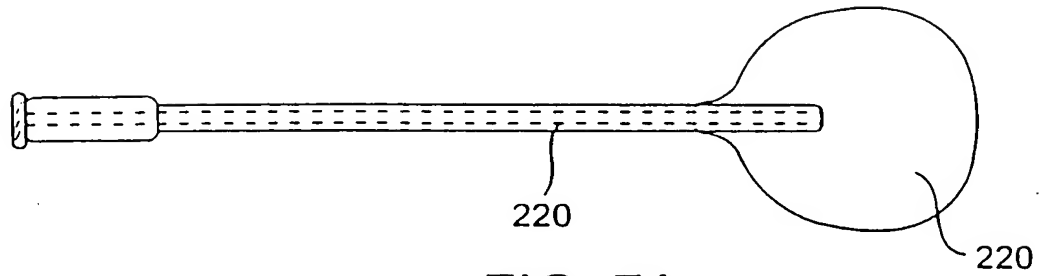


FIG. 7A

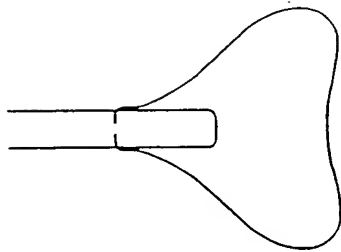


FIG. 7B



FIG. 7C

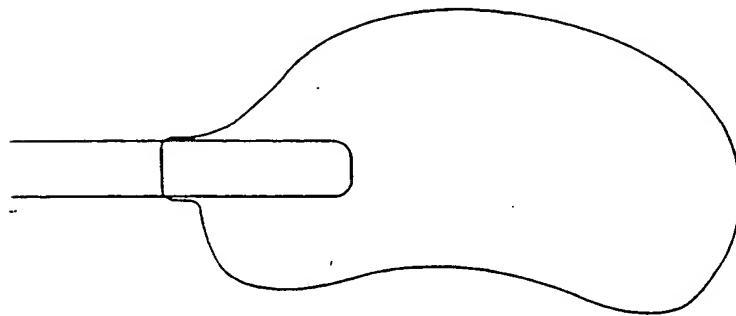


FIG. 7D

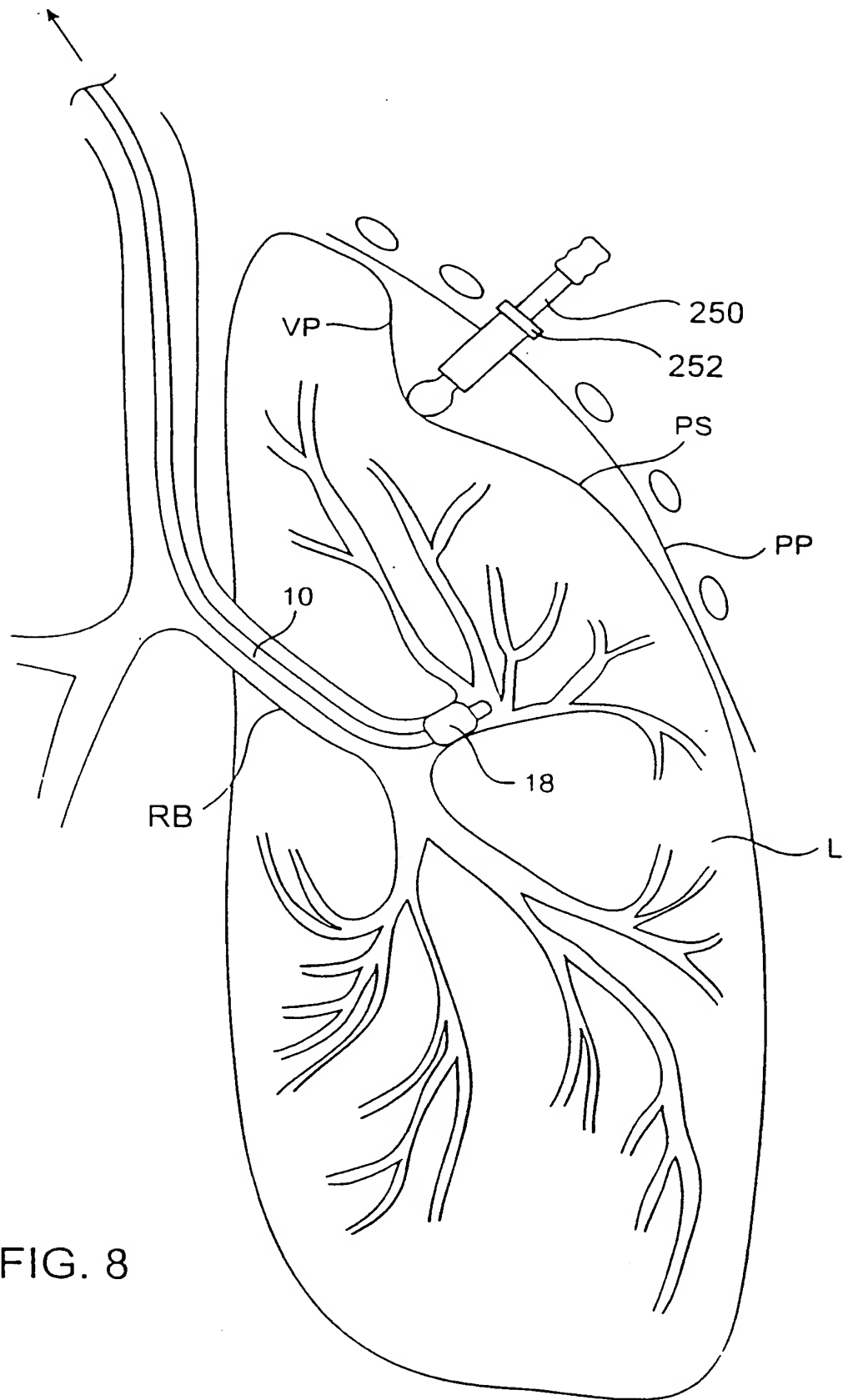


FIG. 8

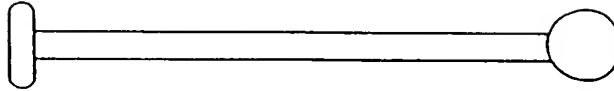


FIG. 9A

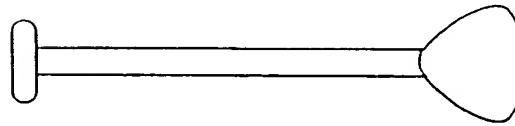


FIG. 9B

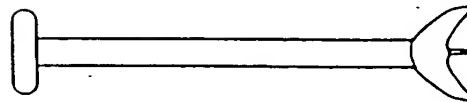


FIG. 9C

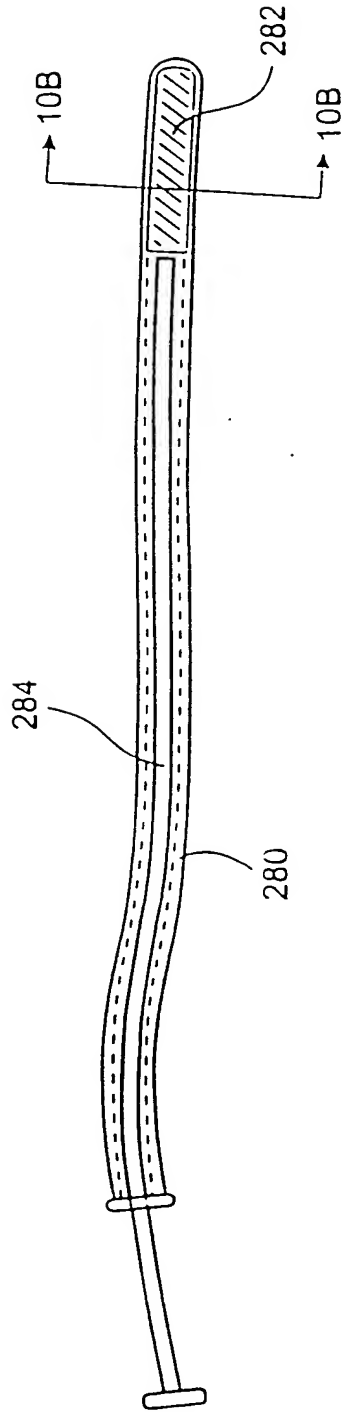


FIG. 10A

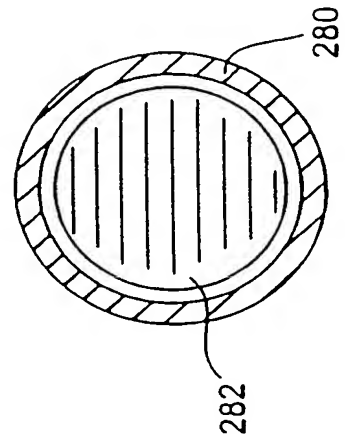


FIG. 10B

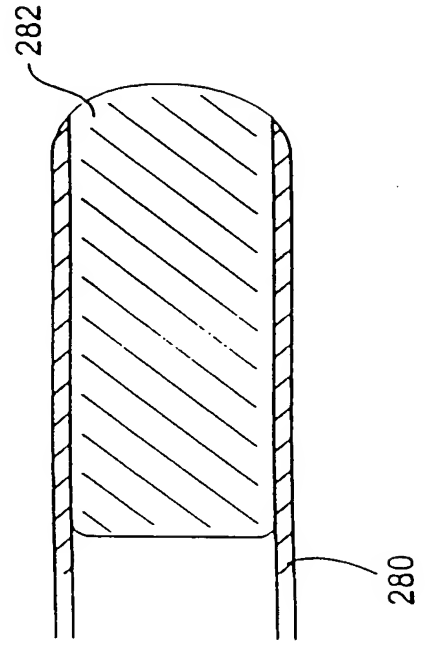
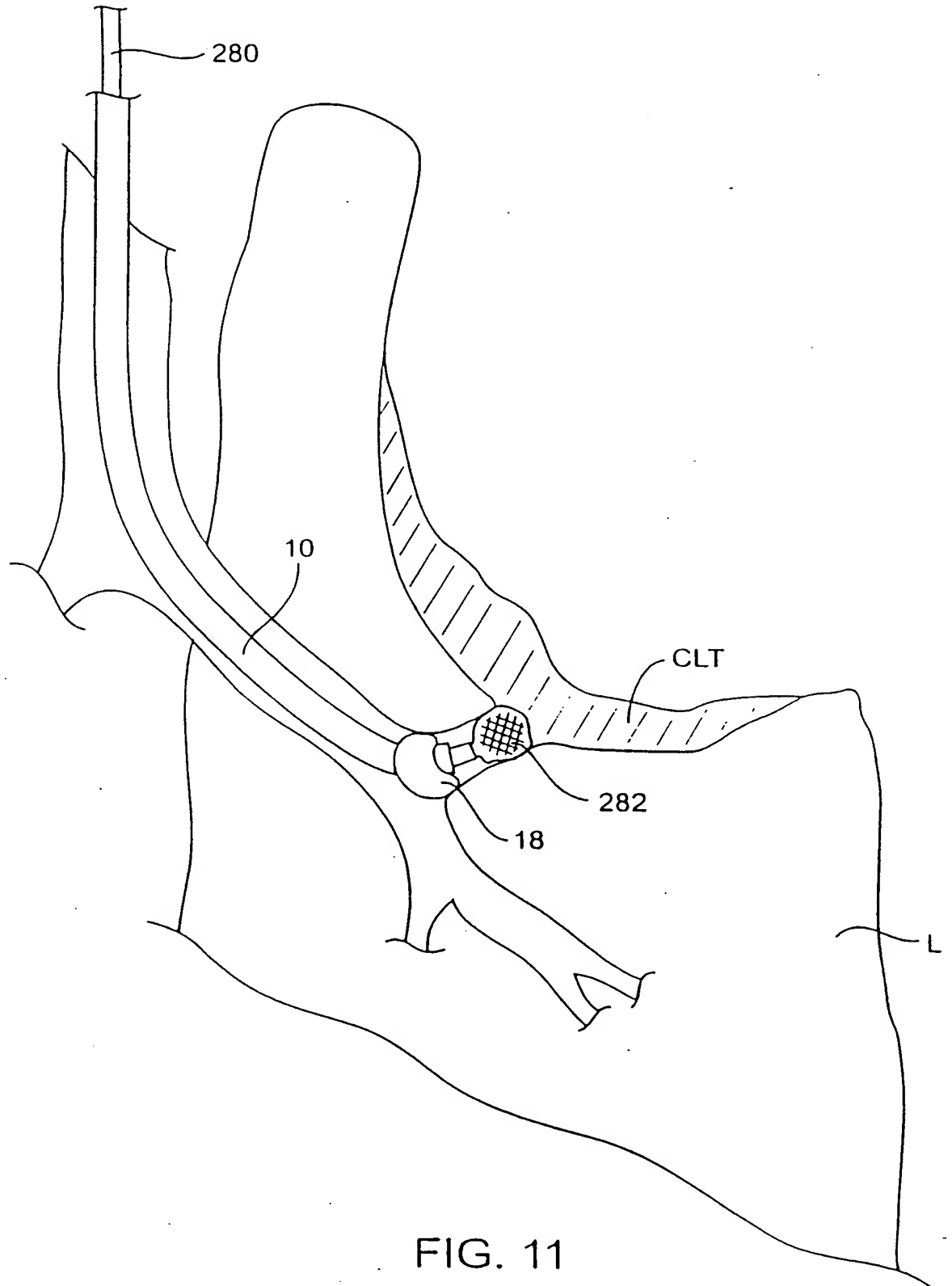
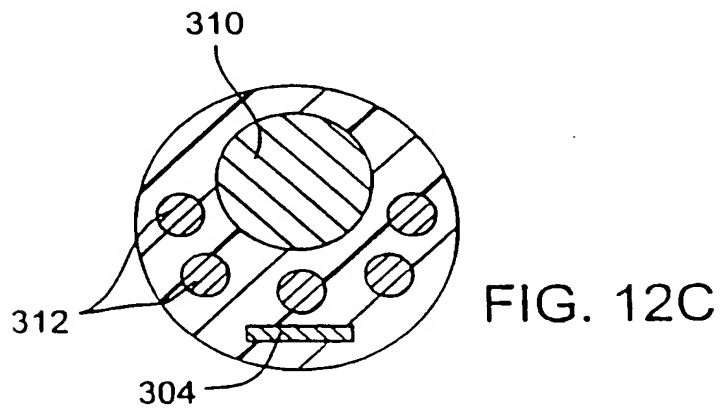
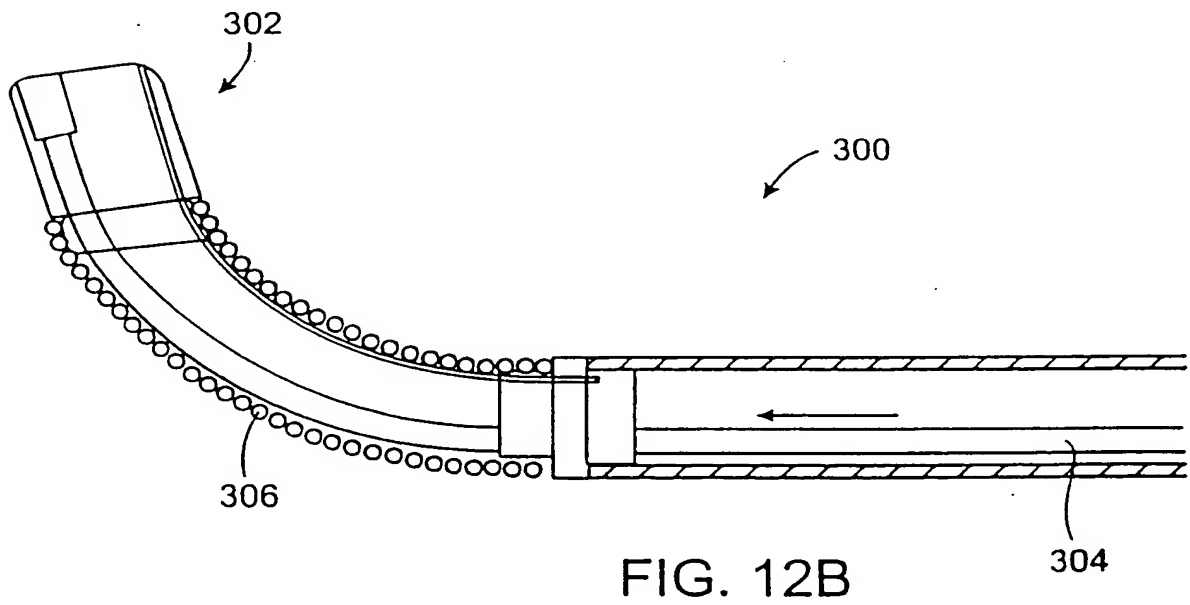
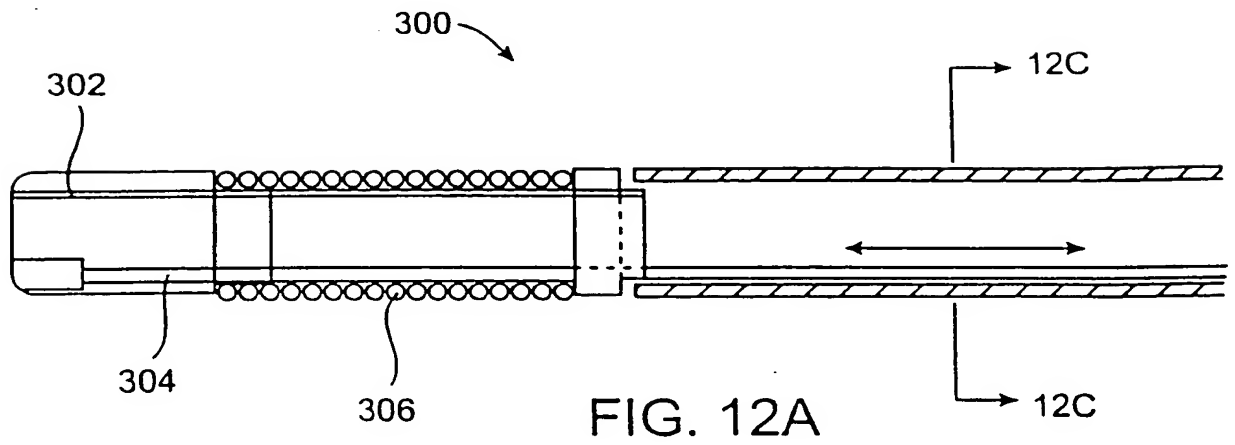


FIG. 10C





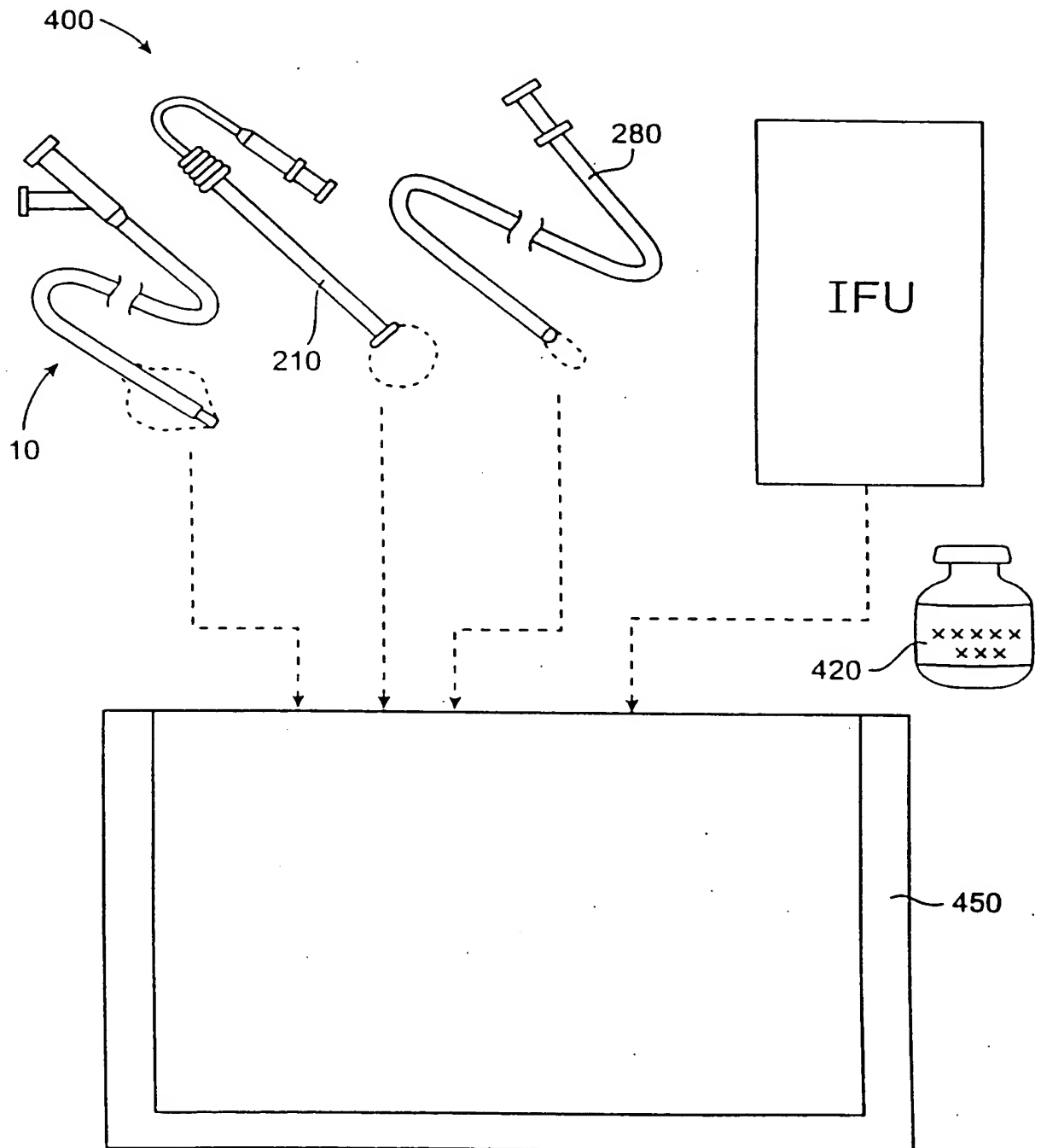


FIG. 13

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